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Mapping the Active Site in a Chemzyme: Diversity in the *N*-Substituent in the Catalytic Asymmetric Aziridination of Imines

Yu Zhang, Zhenjie Lu, Aman Desai, and William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

wulff@chemistry.msu.edu

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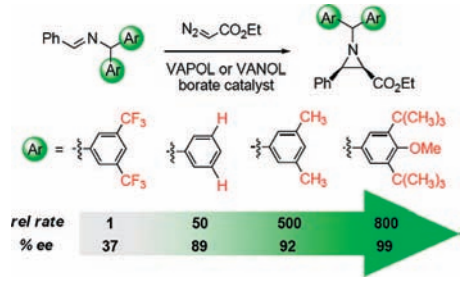
ABSTRACT



The active site of the aziridination catalyst derived from either the VANOL or VAPOL ligand and $B(OPh)_3$ is larger than expected and can accommodate not only significant substitution on the diarylmethyl unit of the imine but also that alkyl (but not perfluorylalkyl) substituents on the aryl groups lead to enhanced rates and enantioselection. The screen of diarylmethyl *N*-substituents on the imine revealed that the 3,5-di-*tert*-butyldianisylmethyl group (BUDAM) gave exceptionally high asymmetric inductions for imines of aryl aldehydes.

One of the truly remarkable observations that was made during the development of the catalytic asymmetric aziridination (AZ reaction) of imines with ethyl diazoacetate was that nearly identical asymmetric inductions were observed for catalysts derived from triphenylborate and either the VANOL or VAPOL ligands.[1,2] This was not true for other reactions involving the VANOL and VAPOL ligands in aluminum- and zirconium-derived catalysts,[3] as their cyclic phosphoric acid catalysts,[4] or as stand alone catalysts,[5] where either VAPOL or VANOL was demonstrated to be superior.

Recent studies have revealed that the reaction of either VANOL or VAPOL with triphenylborate produces a mixture of the mesoborate **6** and the pyroborate **7** (Scheme 1) in favor of the latter, which gives a higher asymmetric induction than the former in the AZ reaction.[1g] Since **7** has two Lewis acidic centers, the question of how imine **1** interacts with the catalyst is suddenly rendered doubly complicated. It is known that the *N*-benzhydryl group in imine **1e** (R = $CHPh_2$) was optimal among the readily available electron-neutral *N*-protecting groups examined in the original screen of the

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(2) The VANOL and VAPOL ligands are now commercially available from Sigma-Aldrich and Strem Chemicals, Inc.

(3) (a) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814–3815. (b) Bao, J.; Wulff, W. D. *Tetrahedron Lett.* **1995**, *36*, 3321–3324. (c) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551–10552. (d) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271–2774. (e) Bolm, C.; Frison, J.-C.; Zhang, Y.; Wulff, W. D. *Synlett* **2004**, 1619–1621. (f) Heller, D. P.; Goldberg, D. R.; Wu, H.; Wulff, W. D. *Can. J. Chem.* **2006**, *84*, 1487–1503.

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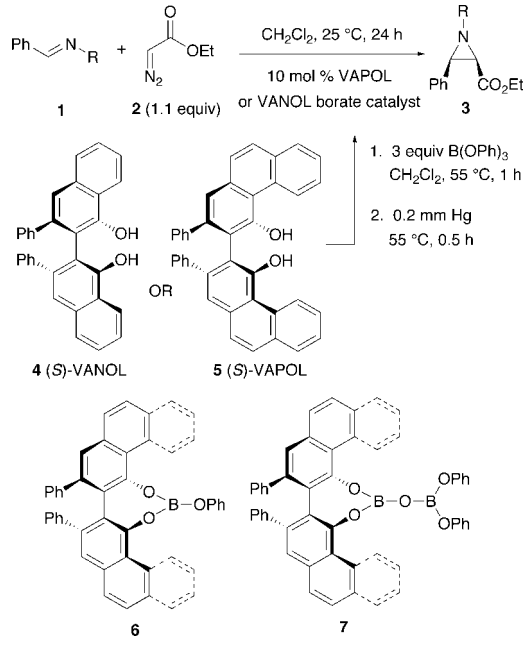
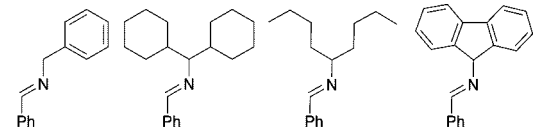
reaction. Thus, in considering how the *N*-benzhydrylimine **1e** will interact with the catalyst, one must include not only Lewis base/Lewis acid interactions but also any potential CH−π interactions[6] and $\pi-\pi$ stacking interactions[7] of the phenyl rings of the benzhydryl group with the arene rings of the ligands. In addition, these interactions should be consistent with the fact that there is little difference between the VANOL- and VAPOL-derived catalysts. In an effort to begin to address these questions, we have undertaken an investigation designed to extensively probe the effects of changes in the conformation, electronics, and sterics of the two phenyl groups in the *N*-benzhydryl substituent. The results of these studies have not only provided a clearer picture of the types of interactions that are important between the catalyst and the imine substrate but also have identified an *N*-substituent that provides exceedingly clean and high-yielding reactions with near-perfect asymmetric inductions for aryl imines in the AZ reaction.

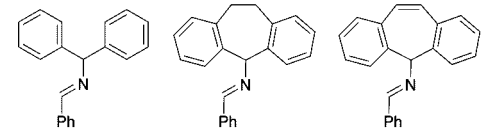
Scheme 1. AZ Reaction



The first set of experiments was designed to probe whether the relative orientation of the two phenyl groups in the *N*-substituent of the imine was important for the binding of the substrate to the active site of the VAPOL catalyst, and the results are summarized in Figure 1. That two phenyl groups are required in the *N*-substituent of the imine is demonstrated by the fact that the AZ reaction of *N*-benzyl imine **1a** gives aziridine **3a** in 51% yield and in only 43% ee with 10 mol % of the (*S*)-VAPOL catalyst under the conditions shown in Scheme 1 (CH_2Cl_2 at room temperature in 24 h). Under the same conditions the benzhydryl imine **1e** gives 83% yield and 89% ee for aziridine **3e**. As controls, the 5-nonylimine **1c** and the dicyclohexylmethyl imine **1b** gave reduced asymmetric inductions compared to benzhydryl imine **1e** and even more noticeably reduced rates (4- and 25-fold, respectively).[8] The reactions with the imines **1d**, **1f**, and **1g** reveal that the orientation of the two phenyl groups is important. Imines **1f** and **1g** both afford higher inductions than the benzhydryl imine **1e**, whereas the fluorenyl imine **1d** gives a lower induction. This suggests that the lower induction for **1d** is not due to the twist angle between the phenyl groups but rather to the degree to which the two phenyl groups are thrust forward toward the ligand when the imine is bound to the catalyst.



imine	**1a**	**1b**	**1c**	**1d**
relative rate	1.7	0.04	0.23	0.3
% Yield **3**	51	18	27	64
% ee **3**	43	74	84	80



imine	**1e**	**1f**	**1g**
relative rate	1.0	1.0	2.2
% Yield **3**	83	75	65
% ee **3**	89	95	96

Figure 1. Diarylmethyl *N*-substituents are optimal.

Favorable non-covalent contacts between arenes include $\pi-\pi$ stacking and CH−π interactions, and both types of contacts are known to be subject to the electronic nature of the substituents on the arene rings.[6,7,9] Thus, in an effort to probe the importance of these effects, a series of electron-rich and electron-poor benzhydryl imines were prepared and evaluated in the AZ reaction (Figure 2). In addition, the size of the binding site of the catalyst is not known, and this was the impetus for the inclusion of a number of 3,5-disubstituted benzhydryl derivatives in the screen. The 10 imines shown in Figure 2 were evaluated in the AZ reaction with both the VANOL- and VAPOL-derived catalysts according to the conditions outlined in Scheme 1, and the isolated yields and asymmetric inductions for the aziridine **3** are indicated in Figure 2. In addition, relative rates were determined for each of the imines. This was done in a pairwise manner in competition experiments in which 1.0 equiv of imine **1e** and 1.0 equiv of a competitor imine (**1h**−**p**) were reacted with

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(6) For a review, see: Nishio, M. *Tetrahedron* **2005**, *61*, 6923–6950.
(7) For recent reviews, see: (a) Janiak, C. *J. Chem. Soc., Dalton Trans.* **2000**, 3885–3896. (b) Roesky, H. W.; Andruh, M. *Coord. Chem. Rev.* **2003**, *236*, 91–119. (c) Bhosale, S.; Sisson, A.; Sakai, N.; Matile, S. *Org. Biomol. Chem.* **2006**, *4*, 3031–3039.
(8) The relative rates were determined as described in Figure 2.
(9) For leading references, see: Bhayana, B.; Wilcox, C. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 6833–6836.

VAPOL catalyst

imine	1h	1i	1j	1k	1e	1l	1m	1n	1o	1p
relative rate	0.02	0.05	0.28	0.45	1.0	2.3	3.8	10.0	11.5	16.3
% Yield **3**	48	63	80	70	83	82	78	89	89	96
% ee **3**	37	86	88	88	89	92	90	95	98	99

VANOL catalyst

imine	1h	1i	1j	1k	1e	1l	1m	1n	1o	1p
relative rate	—	0.10	0.20	—	1.0	—	3.0	8.0	—	6.5
% Yield **3**	73	—	81	89	81	84	91	—	88	97
% ee **3**	75	—	91	91	88	92	93	—	98	99

Figure 2. Relative rates, yields, and asymmetric inductions for the aziridinations of *N*-diarylmethylimines. Aziridination reactions were carried out as indicated in Scheme 1 at 0.5 M in imine. Relative rates studies were carried out in pairwise competitions in CCl_4 with 1 equiv of **1e**, 1 equiv of a competitor imine (**1h**−**1p**), 0.2 equiv of **2**, and 5 mol % of the catalyst at 25 °C for 24 h.

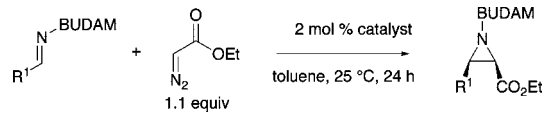
a deficiency of ethyl diazoacetate **2** (0.2 equiv) in the presence of 5 mol % of catalyst in CCl_4 at 25 °C for 24 h. The data reveals that there is a very good correlation between the relative rates and the asymmetric inductions. A general trend was found where more electron-rich phenyl groups gave higher rates and asymmetric inductions than the benzhydryl imine **1e**, and the reverse was observed with electron-withdrawing groups where decreased rates and inductions were observed.

It is quite remarkable that both the VANOL and VAPOL ligands give essentially the same profile in asymmetric induction with the various imines examined in Figure 2. With the exception of the 3,5-bis(trifluoromethyl)-substituted imine **1h**, the difference in asymmetric inductions for the VANOL and VAPOL catalysts is no more than 3% ee across the range of imines. The presence of an *o*-methyl group (imine **1i**) slows the reaction by a factor of 20 (for VAPOL), and the asymmetric induction drops slightly. This is likely due to a steric effect since a methyl group in the para position (imine **1l**) increases the rate by a factor of 2.3 and also increases the asymmetric induction. Interestingly, two methyl groups in the 3- and 5-positions (imine **1n**) increase the rate by a factor of 10 and also increase the asymmetric induction. This is in stark contrast to the 3,5-bis(trifluoromethyl) analogue **1h** which is 500 times slower than imine **1n** and gives the aziridine **3h** in only 37% ee (for VAPOL). This is most consistent with an electronic effect that is presumably due to electrostatic repulsions rather than a steric effect since a CF_3 group is smaller than a *tert*-butyl group and yet the 3,5-di-*tert*-butyl-substituted imine **1p** is in fact the most reactive and selective imine in the screen. The reaction of imine **1p** is 16.3 times faster than the benzhydryl imine **1e** (with VAPOL) and gives the aziridine **3p** in 99% ee and 96−97% yield with both the VANOL and VAPOL ligands.[10]

(10) A catalyst (10 mol %) prepared from (*S*)-BINOL according to the protocol in Scheme 1 will catalyze the AZ reaction of imine **1p** to give aziridine **3p** in 71% yield and 67% ee under the conditions shown in Scheme 1.

The near-perfect performance of the imine **1p** prompted a more thorough study of this family of imines with the tetra-*tert*-butyldianisylmethyl (BUDAM) substituent. The requisite amine from which these imines are prepared is available in four steps and 70% overall yield from 2,6-di-*tert*-butylphenol, which is commercially available at $29/kg (see the Supporting Information). The results of the aziridination reactions of *N*-BUDAM imines prepared from 11 different aldehydes are presented in Table 1. Extremely high asymmetric inductions are observed for all eight of the imines derived from aromatic aldehydes. Although most of the reactions shown in Table 1 are complete in much less time, in an effort to accommodate the range of rates for all the substrates, all reactions were run for 24 h. No effort was made to minimize the reaction time. The reaction of the *N*-BUDAM imine of benzaldehyde **1p** is complete within 20 min with 2 mol % of catalyst in toluene. The reactions of imines with electron-withdrawing groups are complete in less time, while those with electron-donating groups take longer. The reaction of the *p*-methoxyphenyl-substituted *N*-BUDAM imine **10p** is complete within 24 h with 2 mol % of the VAPOL catalyst; however, under the same conditions the corresponding benzhydryl imine **10e** only goes to 73% completion in 24 h with 5 mol % of VAPOL catalyst.[1g] The ^{1}H NMR spectra of the crude mixtures from the reactions of the *N*-BUDAM imines are also extremely clean compared to those from the corresponding benzhydryl imines. The AZ reactions of benzhydryl imines are generally highly cis selective but in some cases significant amounts of the trans aziridine are formed. For example, the reaction of the *o*-bromophenyl benzhydryl imine **11e** gives a 2:1 mixture of *cis*- and *trans*-aziridines,[1g] but in contrast, the *N*-BUDAM imine analogue **11p** gives only the *cis*-aziridine as a single diastereomer with no detectable amount (≤1:50) of the *trans*-aziridine. This is true for all of the imines shown in Table 1. This is also true for the non-cyclized enamine side product which can be formed in the AZ reaction of benzhydryl imines with yields

Table 1. Scope of the BUDAM Imines in the AZ Reaction[a]

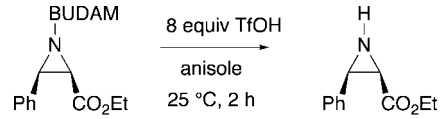


entry	imine	R^1	ligand	aziridine	yield[b] (%)	ee[c] (%)
1	**1p**[d]	C_6H_5	(*S*)-VAPOL	**3p**	98	99
2	**1p**	C_6H_5	(*S*)-VANOL	**3p**	97	98
3	**8p**	2-MeC_6H_4	(*S*)-VAPOL	**18p**	97	99
4	**8p**	2-MeC_6H_4	(*S*)-VANOL	**18p**	96	96
5	**9p**	4-MeC_6H_4	(*S*)-VAPOL	**19p**	95	99
6	**9p**	4-MeC_6H_4	(*S*)-VANOL	**19p**	98	98
7	**10p**	4-$MeOC_6H_4$	(*S*)-VAPOL	**20p**	87	98
8	**10p**	4-$MeOC_6H_4$	(*S*)-VANOL	**20p**	90	98
9	**11p**[e]	2-BrC_6H_4	(*S*)-VAPOL	**21p**	84	96
10	**11p**[e]	2-BrC_6H_4	(*S*)-VANOL	**21p**	83	90
11	**12p**	4-BrC_6H_4	(*S*)-VAPOL	**22p**	99	99
12	**12p**	4-BrC_6H_4	(*S*)-VANOL	**22p**	99	98
13	**13p**[f]	4-$NO_2C_6H_4$	(*S*)-VAPOL	**23p**	92	96
14	**13p**[f]	4-$NO_2C_6H_4$	(*S*)-VANOL	**23p**	91	97
15	**14p**	1-naphthyl	(*S*)-VAPOL	**24p**	93	99
16	**14p**	1-naphthyl	(*S*)-VANOL	**24p**	96	98
17	**15p**	C_2H_5	(*S*)-VAPOL	**25p**	62	93
18	**15p**	C_2H_5	(*S*)-VANOL	**25p**	57	87
19	**16p**[g]	*c*-C_6H_{11}	(*S*)-VAPOL	**26p**	89	89
20	**16p**[g]	*c*-C_6H_{11}	(*S*)-VANOL	**26p**	87	84
21	**17p**[h]	*t*-butyl	(*S*)-VAPOL	**27p**	60[i]	78
22	**17p**[h]	*t*-butyl	(*S*)-VANOL	**27p**	76[j]	80

[a] Unless otherwise specified, all reactions were run at 0.25 M in imine in toluene with 2.0 mmol of imine and 1.1 equiv of ethyl diazoacetate and went to completion with 2 mol % of catalyst at 25 °C for 24 h. Reaction times were not minimized. All imines were purified by crystallization. Cis/trans selectivity was >50:1 in each case as determined by ^{1}H NMR on the crude reaction mixture. [b] Isolated yield after chromatography on silica gel. [c] Determined by HPLC on a Pirkle covalent (R,R)-Whelk-O 1 column. [d] A 97% yield and 99% ee was obtained with reaction time of 20 min (98% conversion observed after 5 min). [e] <2% of enamine product also observed. [f] Imine was 0.22 M in a 5:1 mixture of toluene/CH_2Cl_2. [g] 4 mol % of catalyst. [h] 10 mol % of catalyst. [i] 75% completion. [j] 95% completion.

in the range of <1 to 24%.[1g] The only imine in Table 1 that gave any detectable amount of the enamine side product was the *o*-bromophenyl imine **11p** (<2%). The AZ reactions of all other BUDAM imines shown in Table 1 do not give any detectable amounts of the enamine side product, and in all cases, the ^{1}H NMR spectra of each crude reaction mixture after workup reveals a clean mixture of only the aziridine and the VANOL or VAPOL ligand. The asymmetric inductions for the *N*-BUDAM imines derived from aliphatic aldehydes are not as high as those derived from aromatic aldehydes (entries 17−22). The same has been found to be true for the benzhydryl imines[1g] and also for imines derived from the *N*-dianisylmethyl (DAM) protecting group (series m).[1f] Given the greater surface area of the arene rings in VAPOL compared to VANOL, it is quite astonishing that both ligands give nearly the same asymmetric inductions for each of the imines in Table 1. The average difference in the asymmetric inductions from these two ligands over the 11 substrates is 1.5% ee. The BINOL ligand is not effective for this reaction.[10] Finally, the BUDAM substituent can be removed without causing ring opening to give the *N*-H aziridine in excellent yield employing conditions developed for the *N*-dianisylmethyl (DAM) protecting group (Scheme 2).[1f]

Scheme 2. Deprotection of the BUDAM Group



The data from the screening of the imines **1a**−**p** has provided considerable information on the size and electronic requirements for the *N*-substituent of the imine in the AZ reaction with VANOL and VAPOL catalysts. This study lead to the identification of the tetra-*tert*-butyldianisylmethyl substituent (BUDAM) as clearly superior giving extremely clean and fast reactions with yields and enantioselectivities that make it the most effective catalytic asymmetric aziridination known. Further work will be needed to more precisely determine the nature of the interactions between the imine and catalyst.

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

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