Catalytic Asymmetric Aziridination with a Chiral VAPOL−Boron Lewis Acid

Jon C. Antilla and William D. Wulff*

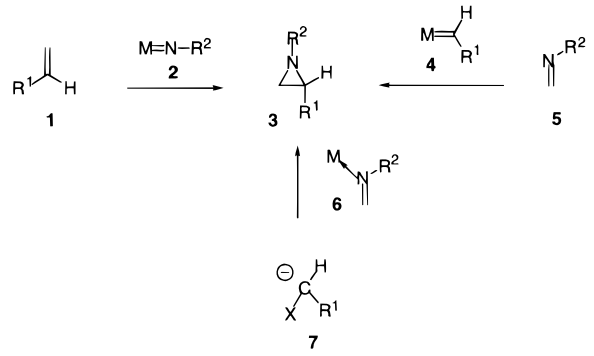
Department of Chemistry, Searle Chemistry Laboratory
The University of Chicago, Chicago, Illinois 60637

Received February 18, 1999

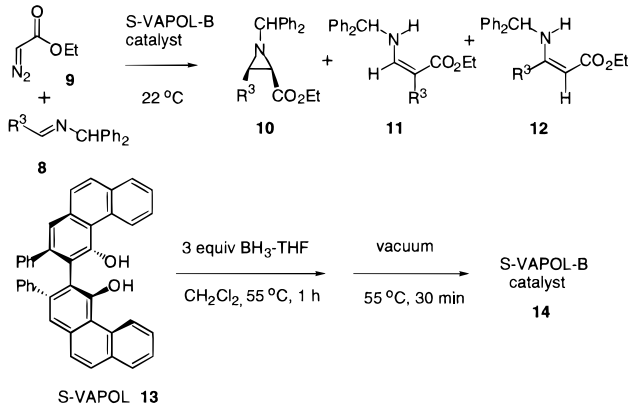
Aziridines are versatile intermediates that have great value in organic synthesis.[1] A recent review on the asymmetric synthesis of aziridines reveals that nearly all nonracemic aziridines are made from other chiral materials.[2] Therefore, there is a need for the development of new methods for the asymmetric catalytic synthesis of aziridines. Previous reports have focused on three different strategies to this problem as outlined in Scheme 1. Most past effort has involved the transfer of a nitrene from [*N*-(*p*-toluenesulfonyl)imino]phenyl iodinane to an alkene mediated by a chiral metal catalyst which can result in the production of *N*-tosyl aziridines in good asymmetric inductions with certain alkene substrates.[3] An alternate method involves the transfer of a carbene to an imine which has been reported with a chiral copper catalyst[4a] and more successfully with a rhodium catalyst that was mediated by a chiral sulfur ylide.[4b] A third strategy arises from the recent observation that simple Lewis acids can catalyze the formation of aziridines from ethyl diazoacetate and imines.[5,6] However, a screen of this reaction with a variety of chiral Lewis acids failed to produce aziridines with significant asymmetric induction.[5c]

Previously we reported that chiral Lewis acid catalysts derived from the vaulted biphenanthrol **13** (VAPOL) proved effective in providing excellent asymmetric inductions in Diels−Alder reactions with both ester and aldehyde dienophiles.[7] We now report that a catalyst prepared from VAPOL and borane−tetrahydrofuran complex can give very high asymmetric inductions in the formation of aziridines from the reaction of benzhydryl imines with ethyl diazoacetate. This catalyst was prepared by treating

Scheme 1



Scheme 2



S-VAPOL with 3 equiv of borane−THF complex, heating at 55 °C for 1 h, removing the volatiles, and then heating the residue at 55 °C for 30 min under a high vacuum[8] (Scheme 2). Entry 4 in Table 1 shows that this catalyst produces a 74% yield of the aziridine **10a** in 98% ee and only small amounts of the acyclic products **11a** and **12a** were observed. The *cis*-aziridine is produced with a diastereoselectivity of greater than 50:1 with the catalyst generated from S-VAPOL but this falls to 8:1 with the catalyst prepared from R-BINOL (entry 1). In addition the enantiomeric excess with the R-BINOL catalyst falls to 17% ee. Entries 2 and 3 in Table 1 reveal that the catalysts that were most effective for Diels−Alder reactions[7] were not optimal for the present aziridination reaction.

The asymmetric induction observed for **10a** is not a function of the substrate-to-catalyst ratio and remains constant as the catalyst loading is reduced from 10 to 1 mol % (entries 5−9). The rate of the reaction significantly drops when the amount of catalyst is reduced from 10 to 2.5 mol %, but interestingly, the rate of the reaction is greatly accelerated if the imine is added by slow addition. Entries 7 and 8 reveal that the order of addition of reagents does not affect the rate. However, the data in entries 7 and 9 reveal that the reaction time can be reduced from 20 to 2 h for reactions with 2.5 mol % catalyst if the imine is added over a period of 1 h.

The rate of the reaction can be affected by the purity of the imines. The reactions in Tables 1 and 2 were performed with imines that were crystallized from ethanol.[9] Imine **8a** contained

(1) (a) Tanner, D., *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 599. (b) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon Press: Oxford, 1996; Vol 1A, pp 1−60. (c) Rai, K. M. L.; Hassner, A. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon Press: Oxford, 1996; Vol 1A, pp 61−96.

(2) Sweeney, J.; Osborn, H. M. I. *Tetrahedron Asymetry* **1997**, *8*, 1693.

(3) (a) Evans, D. A.; Woerpel, Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett*. **1991**, *32*, 7373. (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1993**, *115*, 5326. (d) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc*. **1993**, *115*, 5328. (e) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T., *Synlett* **1993**, 469. (f) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc*. **1994**, *116*, 2742. (g) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett*. **1994**, *35*, 4631. (h) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1995**, *117*, 5889. (i) Nishikori, H.; Katsuki, T. *Tetrahedron Lett*. **1996**, *37*, 9245. (j) Harm, A. M.; Knight, J. G.; Stemp, *Synlett* **1996**, 677. (k) Muller, P.; Baud, C.; Jacquier, Y.; Moran, M.; Nageri, I. *J. Phys. Org. Chem*. **1996**, *9*, 341. (l) Lai, T.-S.; Kwong, H.-L.; Che, C.-M.; Peng, S.-M. *Chem. Commun*. **1997**, 2373. (m) Sodergren, M. J.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3563.

(4) (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 676. (b) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun*. **1995**, 1401. (c) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem*. **1996**, *61*, 8368.

(5) (a) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem*. **1996**, *61*, 8358. (b) Ha, H.-J.; Kang, K.-H.; Suh, J.-M.; Ahn, Y.-G. *Tetrahedron Lett*. **1996**, *37*, 7069. (c) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc. Perkin Trans. 1*, **1997**, 1287. (d) Nagayama, S.; Kobayashi, S. *Chem. Lett.* **1998**, 685.

(6) For other approaches, see: (a) Aires-de-Sousa, J.; Lobo, A. M.; Probhakar, S. *Tetrahedron Lett*. **1996**, *37*, 3183. (b) Verstappen, M. M. H.; Ariaans, G. J. A.; Zwanenburg, B. *J. Am. Chem. Soc*. **1996**, *118*, 8491.

(7) (a) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc*. **1993**, *115*, 3814. (b) Bao, J.; Wulff, W. D. *Tetrahedron Lett*. **1995**, *36*, 3321. (c) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc*. **1996**, *118*, 3392. (d) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc*. **1997**, *119*, 10551.

(8) The same selectivity is observed with a catalyst prepared with 1.0 equiv of borane−THF complex, but catalyst formation requires longer periods of time.

(9) The imines **8a**−**i** were prepared[13] by reaction of benzhydrylamine with 1.0 equiv of aldehyde in methylene chloride at rt in the presence of anhydrous magnesium sulfate. After filtration, the solvent is removed and the imine purifed by crystallization from ethanol with the exception of **8h** which is an oil and was used without purification.

10.1021/ja9905187 CCC: $18.00
Published on Web 05/14/1999

Table 1. Asymmetric Aziridination of Imine **8a** (R^3 = Ph) with (*S*)-VAPOL-Boron Catalyst **14**[a]

entry	catalyst (mol %)	time, h	yield *cis*-**10**[b]	% ee *cis*-**10**[c]	*cis*-**10**/*trans*-**10**[d]	yield **11**[e]	yield **12**[e]
1	10	20	42[f]	17	8:1	8	10
2	10	20	53[g]	66	>50:1	13	6
3	10	18	41[h]	5	>50:1	17	14
4	10	0.5	74	98	>50:1	2	2
5	10	0.5	78[i,j]	97	>50:1	2.5	2.1
6	5	3	74	97.5	>50:1	1.7	0.7
7	2.5	20	73	97	>50:1	1−1.5	1−1.5
8	2.5[k]	17	74	97	>50:1	1.6	1.0
9	2.5[l]	2	79	98	>50:1	≤1	≤1
10	1[l]	16[m]	72	99	42:1	3.7	2.5

[a] Unless otherwise specified, all reactions were run in methylene chloride with 0.1 mmol of (*S*)-VAPOL at 22 °C with 1.1 equiv of ethyl diazoacetate with respect to imine **8**. **9** was added all at once to a mixture of imine and catalyst. Imine **8** was crystallized from ethanol and **9** was used as supplied by Aldrich. Imine concentration is 0.5 M for entries 1−6, and 2.0 M for entries 7−10. [b] Isolated after purification by silica gel chromatography. [c] Determined by HPLC on a Chiralcel OD column. [d] Determined by ^{1}H NMR of crude reaction mixture. [e] Determined by ^{1}H NMR of crude reaction mixture by integration relative to *cis*-**10**. [f] Catalyst prepared from (*R*)-BINOL and BH_3−THF which gave the enantiomer of **10a**. [g] Catalyst prepared from (*S*)-VAPOL and BH_2Br−Me_2S. [h] Catalyst prepared from (*S*)-VAPOL and Et_2AlCl. [i] Reaction with (*R*)-VAPOL which gave the enantiomer of **10a**. [j] 80% recovery of VAPOL. [k] Imine added all at once to a mixture of catalyst and **9**. [l] Imine aded over 3 h by syringe pump to a mixture of the catalyst and **9**. [m] Imine crystallized from CH_2Cl_2/hexane.

Table 2. Asymmetric Aziridination of Imine **8** with (*S*)-VAPOL-Boron Catalyst **14**[a]

entry	imine	R^3	time	yield *cis*-**10**[b]	% ee *cis*-**10**[c]	*cis*-**10**/*trans*-**10**[d]	yield **11**[e]	yield **12**[e]
1	**8a**	Ph	5	77	97	>50:1	≤1	≤1
2	**8b**	p-BrC_6H_4	4	64	97	16:1	3.9	2.0
3	**8c**	*p*-$NO_2C_6H_4$	24	68[f]	91	11:1	≤1	<1
4	**8d**	*p*-$OAcC_6H_4$	16	67	96	40:1	3.6	3.0
5	**8e**	o-MeC_6H_4	24	51[i]	98	3:1	8.1	6.5
6	**8f**	2-Naphthyl	4	70[g,h,i,j]	97	30:1	1.5	1.4
7	**8g**	2-furyl	8	55	94.5	16:1	≤1	≤1
8	**8h**	*n*-Propyl	7	54[f]	91	>50:1	9.6	6.4
9	**8i**	c-C_6H_{11}	3	72	96	35:1	≤1	≤1

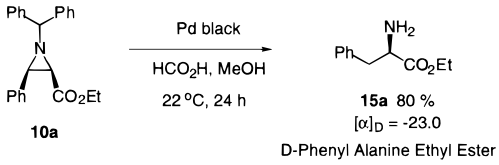
[a] Same as footnote a in Table 1 except solvent is toluene, 10 mol % catalyst is used, and imine is added by syringe pump over 3 h. Imine concentration varies from 0.20−0.50 M. [b−e] See Table 1. [f] Reaction started at 0 °C and warmed to rt after 4−5 h. [g] CH_2Cl_2 as solvent and 5 mol % catalyst. [h] 0.05 mole of VAPOL. [i] 5 mol % catalyst used. [j] Substrate **9** added all at once to a mixture of catalyst and imine.

traces of ethanol as revealed by ^{1}H NMR, but this was only found to be detrimental to the rate with very low catalyst loadings. More reasonable reaction times were observed with 1 mol % catalyst when the imine was purified by crystallization from pentane/CH_2Cl_2. The effect of ethanol was confirmed when the reaction in entry 10 of Table 1 was repeated in the presence of 10 mol % ethanol and found to proceed only to the extent of 18% conversion in 17 h.

This asymmetric aziridination reaction was found to be slightly faster in methylene chloride than in toluene although the latter solvent in some cases gave higher inductions for the *cis*-aziridine and less of the acyclic products **11** and **12**. For this reason, the scope of the reaction was explored in toluene for the substrates listed in Table 2. As can be seen, high enantioselectivities were observed over a range of imine substrates derived from both electron-rich and electron-poor aryl aldehydes and with branched and unbranched aliphatic aldehydes.[10] The reaction times shown in Table 2 are not reflective of rate differences in the imine substrates since the concentrations varied due to solubility and since minimum reaction times were not determined. It was observed that the *p*-bromo and *p*-nitro substituted imines **8b** and **8c** are more reactive than the phenyl imine **8a** under the same conditions. The imine prepared from *p*-methoxy benzaldehyde was slower than imine **8a** and did go to completion in methylene chloride in 24 h, but the aziridine was not stable to purification on silica gel.

The absolute configuration of aziridine **10a** was confirmed by reductive ring-opening to phenyl alanine ethyl ester. Transfer hydrogenation with formic acid lead to selective reduction of the nitrogen-benzyl carbon bond of the aziridine and also to the cleavage of the benzhydryl-protecting group on the nitrogen to give the ethyl ester of phenyl alanine (Scheme 3). The rotation

Scheme 3



of this material was found to be $[\alpha]_D = -23.0$ ($c = 3.2$, EtOH) which is to be compared with the value of $[\alpha]_D = +23.8$ ($c = 3.2$, EtOH) reported for L-phenyl alanine ethyl ester[11] and which is consistent with the fact that the aziridine **10a** used for this reaction was determined to be 99.2% ee by HPLC with a Chiralcel OD column.[12]

The present method allows for the first generally applicable method for the catalytic asymmetric aziridination reaction. Further studies on the scope, mechanism and applications of this process are in progress.

Acknowledgment. This work was supported by the National Institutes of Health. We would like to thank Professor Milton R. Smith, III for helpful discussions and suggestions.

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

JA9905187

(10) Imines derived from pivaldehyde and 1-naphthylaldehyde would not undergo reaction under the conditions in Table 2.

(11) O'Connor, M. J.; Ernst, R. E.; Schoenberrn, J. E.; Holm, R. H. *J. Am. Chem. Soc.* **1968**, 1744.

(12) The enantiomeric excess of the aziridine **10a** can be improved from 97.0 to 99.2% with one crystallization from methylene chloride and pentane.

(13) Armesto, D.; Ortiz, M. J.; Perez-Ossoria, R., *J. Chem. Soc., Perkin Trans. I* **1986**, 2021.