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Direct Access to *N*-H-Aziridines from Asymmetric Catalytic Aziridination with Borate Catalysts Derived from Vaulted Binaphthol and Vaulted Biphenanthrol Ligands

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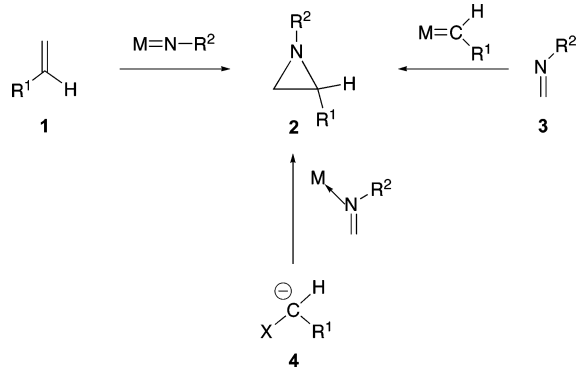
Abstract: The asymmetric catalytic aziridination reaction (AZ reaction) of *N*-dianisylmethylimines (*N*-DAM-imines) with ethyl diazoacetate is developed with chiral catalysts prepared from triphenylborate and both the vaulted binaphthol (VANOL) and vaulted biphenanthrol (VAPOL) ligands. Catalysts derived from both ligands were equally effective in terms of asymmetric induction, but the VANOL catalyst was slightly faster. Up to 400 turnovers could be achieved with the VANOL catalyst while still maintaining ≥90% ee in the aziridine product. The ligand could be recovered in 95% yield with no loss in optical purity. Excellent asymmetric inductions were observed with arylimines, and although slightly lower inductions were observed for alkyl-substituted imines, the optical purity of the aziridines from all of the imine substrates could be enhanced to ≥99% ee with a single crystallization. Methods were developed for deprotection of the *N*-DAM-aziridines under acidic conditions without causing an acid-promoted opening of the ring. Excellent yields of the *N*-H-aziridines could be obtained with both alkyl- and aryl-substituted aziridines. Finally, activation of the *N*-H-aziridines was achieved with Boc, tosyl, and Fmoc groups. The activated aziridines can be converted to β^3-amino esters, and unexpectedly, the *N*-Boc-protected aziridine-2-carboxylate **16b** with a phenyl substituent in the 3-position cis to the ester group was found to undergo ring expansion to a mixture of *cis*- and *trans*-oxazolidinones.

Introduction

The strain energy of an aziridine plays a lead role in the interest in this class of compounds as synthetic intermediates. As a consequence, a substantial body of work has been accumulated that addresses both their synthesis and ring-opening reactions.[1] One aspect of their synthesis that is still lacking is reliable methods for their asymmetric synthesis from nonchiral precursors.[2−4] There are three different strategies that have been pursued with regard to the development of asymmetric catalytic methods for the synthesis of aziridines (Scheme 1). The first success in the metal nitrene approach was reported simultaneously by Evans et al.[5a] and Jacobsen and co-workers.[5b] The scope of these reactions was limited, with each report including only a single substrate that gave greater than 90% ee. Although several ligand modifications have been made that resulted in different substrate specificity, no general asymmetric aziridination reactions have been developed around the Jacobsen or Evans systems. The best system developed to date around the metal nitrene approach is that by Katsuki and co-workers,[4p] who recently reported that a highly modified salen ligand could be used to provide high asymmetric inductions (85−99% ee) with a number of vinyl arenes. Aliphatic alkenes gave good inductions but low yields (20−30%). Thus the development of a catalyst with broader substrate scope remains an actively pursued goal. A second and complementary approach involves the asymmetric addition of a carbene to an imine. The first and only real success with this approach involves an ylide transfer to an imine, which is part of an exceptionally cleverly designed double-catalytic cycle developed by Aggarwal and co-workers,[4h,6] involving the intermediacy of a chiral sulfur ylide. High asymmetric inductions could be obtained by this method. The shortcomings of the method include the fact that only modest

Scheme 1



(1) For recent reviews, see (a) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599. (b) McCoull, W. M.; Davis, F. A. *Synthesis* **2000**, *10*, 1347. (c) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (e) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979. (f) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*. 247.

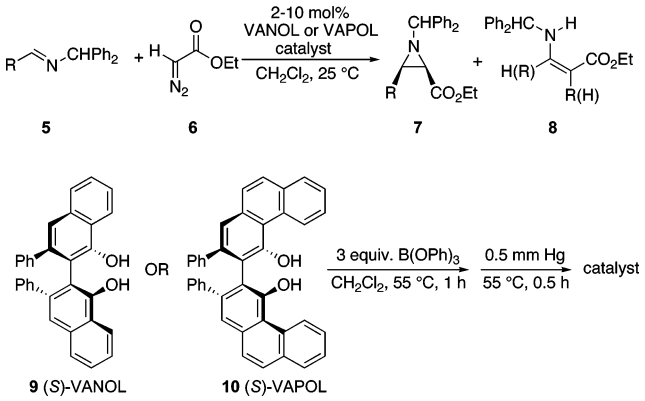
(2) For a review of catalytic asymmetric aziridinations up to 2003, see Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(3) For a review of catalytic asymmetric additions to imines, see Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315.

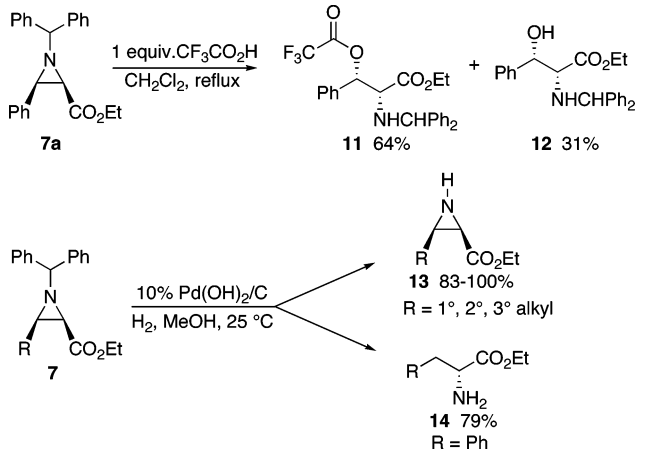
control of the cis/trans selectivity of the aziridines could be achieved and 20 mol % of the chiral sulfide is required. A third approach involves the activation of an imine by a chiral Lewis or Bronsted acid toward reaction with a carbenoid. It is this latter approach that has been the focus of this laboratory over the past few years.[7]

While it has been known for some time that Lewis acids can effect the formation of aziridines from imines and diazo compounds, it was not until the work of Brookhart and Templeton and co-workers[8a] and later by Jorgensen and co-workers[8b,c] that the generality of this process was appreciated. With the information in these reports, it was found that catalysts derived from triphenylborate and either vaulted binaphthol (VANOL) or vaulted biphenanthrol (VAPOL) were effective in catalyzing the formation of *cis*-aziridine-2-carboxylates from *N*-benzhydrylimines and ethyl diazoacetate (Scheme 2).[7b] This asymmetric aziridination reaction (AZ reaction) proved to be general for imines derived from aromatic and aliphatic aldehydes giving the aziridine **7** with high cis/trans ratios in good to high yields with excellent enantioselective induction. A very surprising aspect to this reaction is that the VANOL- and VAPOL-derived catalysts were essentially equally effective in providing asymmetric induction for each imine examined. This is in contrast to other reactions where either the VANOL- or VAPOL-derived catalyst was more effective,

Scheme 2



Scheme 3



and in no other case was such a nearly identical profile observed.[9,10]

Many of the optically active benzhydrylaziridines **7** that we have considered for various synthetic applications would require removal of the *N*-benzhydryl group to form *N*-H-aziridine **13** (Scheme 3) and reprotection with an electron-withdrawing group on the nitrogen. Thus, for maximum versatility, there would be a need for deprotection methods that would allow for the clean conversion of benzhydrylaziridines **7** to *N*-H-aziridines **13**. Alternatively, a better solution would be to perform the reaction with an imine already bearing an electron-withdrawing group on the nitrogen. However, it was found that the benzhydryl group was essential for achieving high asymmetric inductions in these reactions. Efforts to replace the benzhydryl on the imine with a benzyl group, a trityl group, or to employ diphenylphosphinoylimines or diphenylhydrazones led to either low reactivity or low asymmetric induction.

The most common method for deprotection of *N*-benzhydrylamines is treatment with acid, and this is also viable for certain *N*-benzhydrylaziridines.[11] However, aryl-substituted *N*-benzhy-

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(9) The VANOL and VAPOL ligands are now commercially available from Sigma−Aldrich Corp. and Strem Chemicals, Inc.

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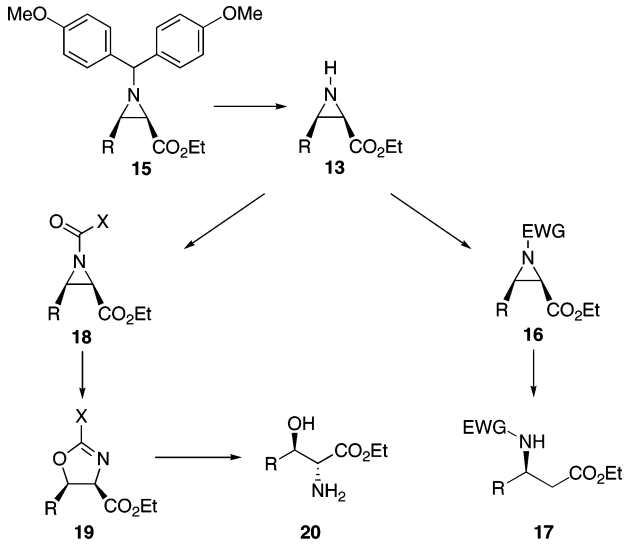
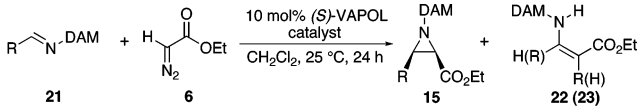
Scheme 4



drylaziridines are much more susceptible to acid-promoted aziridine opening.[7b−d] For example, treatment of ethyl *N*-benzhydryl-3-phenylaziridine-2-carboxylate **7a** with trifluoroacetic acid resulted in the isolation of a single diastereomer of the ring-opened product **11** and some of the deacylated product **12** (Scheme 3). Formation of **11** resulted from inversion at the C-3 carbon as revealed by an X-ray structure of the salt of **12** with TFA (see Supporting Information).[12] In previous work, we reported that the method of choice for removal of the benzhydryl group from 3-alkyl-substituted aziridines was reductive cleavage with Pearlman's catalyst.[13] However, as with other hydrogenative methods, the cleavage of the benzhydryl group from the 3-arylaziridine **7a** (R = Ph) could not be effected without also opening the aziridine ring to give **14** (Scheme 3).

In an endeavor to find a protecting group for the nitrogen of aziridines that could be globally effective for all aziridines, allowing for its removal in high yield and for access to *N*-H-aziridines without any ring-opening side reactions, attention was turned to the dianisylmethyl (DAM) protecting group.[11] It was anticipated that the acid-mediated cleavage of the DAM group would be much more facile than that of the benzhydryl group from a consideration of relative stability[14] of the two diarylmethyl cations that would be formed. Two questions arise from this consideration: (1) Would the increased electron stabilization of the DAM cation be enough to overcome the natural tendency of an aryl-substituted aziridine to undergo ring opening upon treatment with acid? (2) Would the AZ reaction with *N*-DAM-imines still provide high yields and asymmetric inductions? We report herein a highly enantio- and diastereoselective aziridination reaction of *N*-DAM-protected imines with ethyl diazoacetate mediated with either VANOL- or VAPOL-derived catalysts. Cleavage of the DAM group can be achieved under mildly acidic conditions to give cis-substituted *N*-H-aziridines in excellent yield and with no erosion of stereochemistry or evidence of ring-opened products (Scheme 4). It will also be shown that these aziridines can be activated with the proper N-substituent and induced to undergo a Lewis acid-mediated ring expansion to give oxazolidinones[15] and a SmI_2-mediated *C*2-reductive ring opening to give β-amino esters.

Table 1. Asymmetric Aziridination of *N*-DAM-Imines **21** with VAPOL Catalyst in CH_2Cl_2[a]



21 **6** **15** **22 (23)**

DAM = dianisylmethyl

entry	series	R	% yield *cis*-**15**[b]	% ee *cis*-**15**[c]	*cis*:*trans*-**15**[d]	% yield **22**[e]	% yield **23**[e]
1	a	*c*-C_6H_{11}	65	67	25:1	3	1
2	b	*t*-Bu	58	80	33:1	1	1
3	c	*n*-Pr	10	nd	nd	nd	nd
4	d	Ph	83	91	33:1	1	1
5	e	*o*-MeC_6H_4	76	79	33:1	4	1
6	f	*p*-BrC_6H_4	87	87	25:1	1	1
7	g	*p*-$NO_2C_6H_4$	81	85	15:1	1	1
8	h	*p*-$OMeC_6H_4$	45[f]	89	50:1	1	1
9	i	1-naphthyl	83	93	20:1	1	1

[a] Unless otherwise specified, all reactions were performed with 10 mol % catalyst in CH_2Cl_2 at 0.5 M in **21** with 1.1 equiv of **6** at 25 °C for 24 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined on purified *cis*-**15** by HPLC on a Chiralpak AD column. [d] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^1H NMR spectrum of the crude reaction mixture. [e] Determined by integration of the NH signals of **22** and **23** relative to the methine proton of *cis*-**15** in the ^1H NMR spectrum of the crude reaction mixture. [f] Reaction time was 72 h, at which time 50% conversion was observed. Purification of *cis*-**15h** was achieved on Et_3N-treated silica gel.

Results and Discussion

Asymmetric Aziridination. The series of *N*-DAM-imines **21a**−**i** were prepared[16] and surveyed in a study of the AZ reaction with ethyl diazoacetate, and the results are presented in Table 1. The catalyst was prepared from VAPOL and triphenylborate according to our previously published procedure (Scheme 2) (see Supporting Information).[7b] The asymmetric inductions observed were slightly lower for aryl-substituted imines than they were for the corresponding benzhydrylimines and even lower for aliphatic-substituted imines. The cis/trans selectivities were comparable, as were the yields, except for those observed for the reactions of the aliphatic imines, especially the imine of butanal, where a very slow reaction was observed (Table 1, entry 3). The amount of enamine side products was less than was observed with the benzhydrylimines. The AZ reaction of imine **21h** derived from *p*-methoxybenzaldehyde was quite slow, requiring 72 h for 50% completion. The resulting aziridine **15h** was sensitive to hydrolysis and could be purified only if the silica gel was pretreated with triethylamine.

In an effort to improve the asymmetric inductions for the AZ reaction of the *N*-DAM-imines, reaction of the cyclohexyl and phenyl derivatives **21a** and **21d** were examined in various

(12) We suspect that product **12** resulted from hydrolysis during the silica gel chromatographic purification of **11**. See Supporting Information for details.
(13) Patwardhan, A. P.; Lu, Z.; Pulgam, V. R.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 2201.
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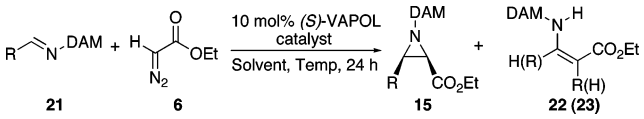
(16) The imines were prepared and purified by crystallization except the imine **21c**, which was used in crude form. See Supporting Information for details.

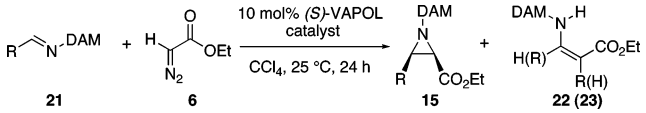
Table 2. Optimization for Asymmetric Aziridination of *N*-DAM-Imines **21a** and **21d**[a]



entry	series	R	solvent	temp (°C)	% yield *cis*-**15**[b]	% ee *cis*-**15**[c]	*cis*:*trans*-**15**[d]	% yield **22**[e]	% yield **23**[e]
1	a	*c*-C_6H_{11}	CH_2Cl_2	25	65	67	25:1	3	1
2[f]	a	*c*-C_6H_{11}	toluene	25	58	52	25:1	12	7
3	a	*c*-C_6H_{11}	CCl_4	25	69	77	50:1	3	1
4[f]	a	*c*-C_6H_{11}	CCl_4	0	45	19	33:1	4	1
5	d	Ph	CH_2Cl_2	25	83	91	33:1	1	1
6	d	Ph	toluene	25	88	95	50:1	1	1
7	d	Ph	CCl_4	25	91	96	50:1	1	1
8	d	Ph	CCl_4	0	91	97	33:1	1	1

[a] Unless otherwise specified, all reactions were performed with 10 mol % catalyst at 0.5 M in **21** with 1.1 equiv of **6** for 24 h. [b−e] See footnotes in Table 1. [f] Imine **21a** was not completely dissolved.

Table 3. Asymmetric Aziridination of *N*-DAM-Imines **21** with VAPOL Catalyst in CCl_4[a]



entry	series	R	% yield *cis*-**15**[b]	% ee *cis*-**15**[c]	*cis*:*trans*-**15**[d]	% yield **22**[e]	% yield **23**[e]
1	a	*c*-C_6H_{11}	69	77	50:1	3	1
2	b	*t*-Bu	47	75	50:1	1	1
3	b	*t*-Bu	74[f]	87	50:1	1	1
4	c	*n*-Pr	11	63	nd	nd	nd
5	d	Ph	91	96	50:1	1	1
6	e	*o*-MeC_6H_4	86	89	50:1	1	1
7	f	*p*-BrC_6H_4	92	93	50:1	1	1
8	f	*p*-BrC_6H_4	89[g]	97	33:1	1	1
9	g	*p*-$NO_2C_6H_4$	88	96	20:1	1	1
10	h	*p*-$MeOC_6H_4$	49[h]	nd	nd	nd	nd
11	i	1-naphthyl	92	94	50:1	1	1

[a] Unless otherwise specified, all reactions were performed in CCl_4 at 0.1−0.5 M in imine with 10 mol % catalyst and 1.1 equiv of **6** at 25 °**C** for 24 h. nd = not determined. [b−e] See footnotes in Table 1. [f] Reaction in 3:1 CCl_4/CH_2Cl_2. [g] Reaction in 7:1 CCl_4/CH_2Cl_2. [h] Reaction time was 3 days, which gave 70% conversion. Isolation was achieved with Et_3N-treated silica gel. The isolated yield was ∼10% with untreated silica gel.

solvents (Table 2). Each imine was screened in toluene, methylene chloride, and carbon tetrachloride at room temperature or 0 °C. There was significant improvement in the asymmetric induction of cyclohexylimine **21a** in carbon tetrachloride as compared to methylene chloride; however, the induction dropped dramatically in entries 2 and 4 for those reactions where the imine **21a** was not completely dissolved. The reaction of phenylimine **21d** in toluene gives 95% ee and the induction with this imine in carbon tetrachloride could be increased over that of the reaction in methylene chloride and toluene, and the yield was slightly improved as well. The reactions with phenylimine **21d** in both toluene and carbon tetrachloride gave very high diastereoselectivity, and the overall formation of the noncyclized enamine products **22** and **23** was 2% in each case.

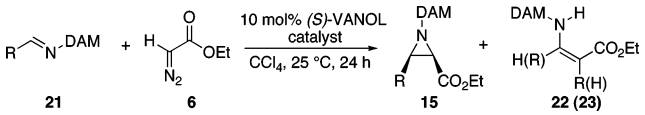
The AZ reaction of *N*-DAM-imines **21a**−**h** with the VAPOL catalyst was reexamined in carbon tetrachloride, and the results are presented in Table 3. The asymmetric inductions were uniformly improved over those in methylene chloride, and the yields are better in each case as well (Table 1 vs Table 3). The cis/trans selectivities are also higher in CCl_4. This type of observation is normally the case for these aziridination reactions: the cis/trans selectivity usually increases as the asymmetric induction increases. Of importance to note from the data in Table 3 is that the asymmetric inductions for the aryl-substituted imines are excellent, however, the inductions for the aliphatic imines are lower and, in addition, the reaction with the imine of *n*-butanal is very slow. Reaction of the *p*-methoxyphenylimine **21h** is also slow but is slightly faster in CCl_4 than in CH_2Cl_2 (Table 3, entry 10, vs Table 1, entry 8). The imines in many cases are less soluble in toluene and carbon tetrachloride than they are in methylene chloride; therefore, some reactions were also examined in a mixed solvent of carbon tetrachloride and methylene chloride (Table 3, entries 3 and 8).[17]

The AZ reaction of benzhydrylimines with the catalyst prepared from triphenylborate and the VAPOL ligand gives a profile for asymmetric induction that is nearly identical to that for the same catalyst generated from the VANOL ligand. This also proved to be the case for the aziridination with *N*-DAM-imines in carbon tetrachloride (Table 4). However, it was noted that the reactions with the VANOL catalyst appear to be slightly faster. For example, reaction of the *p*-methoxyphenylimine **21h** went to completion in 24 h with the VANOL catalyst (Table 4, entry 9), whereas the same imine with the VAPOL catalyst went to only 70% conversion in 3 days (Table 3, entry 10). In addition, the yields and diastereoselectivities were typically higher for VANOL-catalyzed reactions of aryl-substituted imines. The asymmetric induction dropped for *p*-bromophenyl- and 1-naphthylimines, but this could be recovered if the reactions were performed at lower temperatures (Table 4, entries 6, 7, and 11). Each *N*-DAM-aziridine in Table 4 could be crystallized to ≥99% ee with a single crystallization from methylene chloride and hexanes. For example, the cyclohexyl-substituted aziridine **15a** could be obtained in >99% ee in 68% overall yield from the imine **21a**, and the phenyl-substituted aziridine **15d** could be obtained in >99% ee in 85% overall yield from the imine **21d**.

The rate of reaction of *p*-methoxyphenyl-substituted *N*-DAM-imine **21h** was faster with the VANOL catalyst than with the VAPOL catalyst (Table 4, entry 9, vs Table 3, entry 10). This makes sense if the rate-limiting step is the attack of the diazo compound on the imine, which is activated by coordination to

(17) In each case, just enough methylene chloride was added to effect complete dissolution of the imine and the concentration was adjusted accordingly.

Table 4. Asymmetric Aziridination of *N*-DAM-Imines **21** with VANOL Catalyst in CCl_4[a]

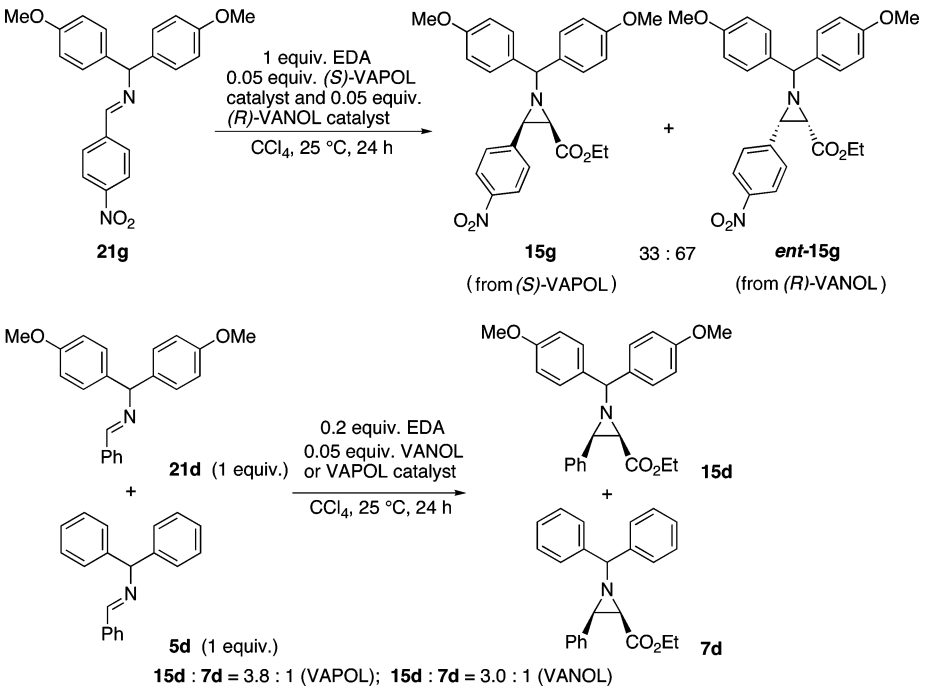


21 **6** **15** **22 (23)**

entry	series	R	% yield *cis*-**15**[b]	% ee *cis*-**15**[c]	% yield *cis*-**15**[d]	% ee *cis*-**15**[c,e]	*cis*:*trans*-**15**[f]	% yield **22**[g]	% yield **23**[g]
1	a	*c*-C_6H_{11}	86	84	68	>99	33:1	7	2
2	b	*t*-Bu	70	75	39	99	50:1	6	19
3	d	Ph	92	95	85	>99	33:1	1	1
4	e	*o*-MeC_6H_4	80	89	75	99	50:1	3	1
5	f	*p*-BrC_6H_4	89	80	nd	nd	50:1	1	1
6[h]	f	*p*-BrC_6H_4	95	90	nd	nd	50:1	1	1
7[i]	f	*p*-BrC_6H_4	95	93	86[j]	>99[j]	50:1	1	1
8	g	*p*-$NO_2C_6H_4$	97	97	76[k]	>99[k]	50:1	1	1
9	h	*p*-$MeOC_6H_4$	80	95	nd	nd	50:1	1	1
10	i	1-naphthyl	98	86	nd	nd	50:1	1	1
11[h]	i	1-naphthyl	91	97	82	>99	50:1	2	1

[a] Unless otherwise specified, all reactions were performed with 10 mol % catalyst with 1.1 equiv of **6** at 25 °**C** for 24 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined on purified *cis*-**15** by HPLC on a Chiralpak AD column. [d] Overall yield after chromatography and a single crystallization from CH_2Cl_2/hexanes (see text for details). [e] This % ee was determined after chromatography and a single crystallization from CH_2Cl_2/hexanes (see text for details). [f] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^1H NMR spectrum of the crude reaction mixture. [g] Determined by integration of the NH signals of **22** and **23** relative to the methine proton of *cis*-**15** in the ^1H NMR spectrum of the crude reaction mixture. [h] Reaction temperature was 0 °C for 5 h and then 25 °C for 19 h. [i] Reaction temperature was −10 °C for 5 h and then 25 °C for 19 h. [j] Overall yield and % ee were determined after chromatographic purification of **15f** and then conversion to **13f** and crystallization. [k] Overall yield and % ee were determined after chromatographic purification of **15g** and subsequent conversion to the unprotected aziridine **13g**, followed by protection as its Boc-protected aziridine, and finally a crystallization.

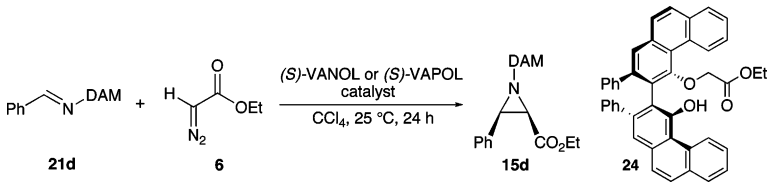
Scheme 5



the catalyst. An experiment was designed to quantify this rate difference between the two ligands and is shown in Scheme 5. The aziridination of *p*-nitrophenyl-substituted imine **21g** was carried out with a mixture of 5 mol % catalyst derived from (*R*)-VANOL and 5 mol % catalyst derived from (*S*)-VAPOL. Imine **21g** was chosen for this competition because it gave very high induction with both catalysts (96−97% ee; Table 3, entry 9, and Table 4, entry 8). This competition produced a 1:2 mixture of **15g** and *ent*-**15g**, thus revealing that the catalyst from VANOL is twice as fast as the VAPOL catalyst. This experiment was designed with the knowledge that neither VANOL nor VAPOL catalyst formed with $B(OPh)_3$ exhibits any nonlinear effects and thus each catalyst is deemed likely to contain only one molecule of the ligand.[18] Information was also sought on the relative reactivity of the *N*-DAM-imines **21** versus the benzhydrylimines **5**. To this end, a competition was set up between the two imines. To a 1:1 mixture of the imines **21d** and **5d** were added 0.2 equiv of ethyl diazoacetate and 5 mol % of either VANOL or VAPOL catalyst. Surprisingly, *N*-DAM-imine **21d** reacted 3.8 times faster than benzhydrylimine **5d** with the VAPOL catalyst and 3.0 times faster with the VANOL catalyst (Scheme 5). One might have expected that the more

(18) Zhang, Y.; Wulff, W. D., unpublished results.

Table 5. Catalyst Loading Study of *N*-DAM Imine **21d** with VANOL or VAPOL Catalysts[a]



21d **6** **15d** **24**

				crystallized **15d**		recrystallized **15d**			overall (**15d**)	
entry	**21d** (mmol)	ligand	loading (mol %)	yield[b] (%)	ee[c] (%)	yield[d] (%)	ee[c] (%)	ee of mother liquor[c,e] (%)	yield[f] (%)	ee[c,g] (%)
1	1	(*S*)-VAPOL	10	nd	nd	nd	nd	nd	91	96
2	1	(*S*)-VANOL	10	nd	nd	nd	nd	nd	92	95
3[h]	20	(*S*)-VAPOL	2	79	>99	nd	nd	73	95	96
4	10	(*S*)-VAPOL	1.0	89	92	76	98	81	89	96
5	10	(*S*)-VANOL	1.0	90	93	78	98	81	92	96
6	20	(*S*)-VAPOL	0.5	79	96	72	98	73	82	95
7	30	(*S*)-VANOL	0.5	79	91	68	98	72	92	92
8[i]	40	(*S*)-VAPOL	0.25	69	86	54	89	82	72	87
9	35	(*S*)-VANOL	0.25	76	90	66	97	65	89	90

[a] Unless otherwise specified, all reactions were performed in CCl_4 at 0.5 M in **21d** with 1.1 equiv of **6** at 25 °C for 24 h; *cis*-**15d**/*trans* **15d** ≥ 33:1, nd = not determined. [b] Yield based on **21d** after crystallization from a 1:5 mixture of CH_2Cl_2/hexanes. [c] Determined by HPLC on a Chiralpak AD column. [d] Yield based on **21d** after two crystallizations from a 1:5 mixture of CH_2Cl_2/hexanes. [e] Measured on the product **15d** obtained by silica gel purification of residue obtained from the combined mother liquors from the first and second crystallizations. [f] Combined yield of recrystallized product **15d** and of **15d** obtained by silica gel chromatographic purification of residue obtained from the combined mother liquors. [g] Calculated from the combined data of the recrystallized product and the product that was obtained by silica gel chromatographic purification of residue obtained from the combined mother liquors. [h] 95% recovery of (*S*)-VAPOL (see Supporting Information). [i] 80% conversion after 48 h.

electron-rich *N*-DAM-imine would have been more sluggish. An explanation of the increased reactivity of *N*-DAM imines relative to the benzhydrylimines will have to await further studies focused on the structure and mechanism of the catalyst. The reason for the increased rate of reaction with the VANOL catalyst versus the VAPOL catalyst is also not clear at this point; however, it suggests that lower catalyst loadings may be possible for the VANOL catalyst.

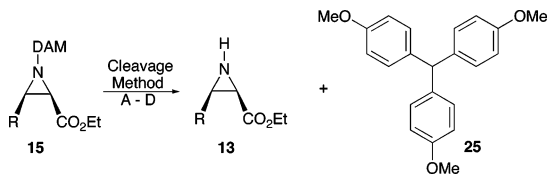
The above results prompted a study on catalyst loading to determine the maximum turnover for these catalysts. The study was undertaken on phenylimine **21d** with both VANOL- and VAPOL-derived catalysts. The reactions were carried out in carbon tetrachloride at room temperature for 24 h, and all of the reactions indicated in Table 5 except entry 8 (80% conversion) went to completion under these conditions. It was found that the amount of both the VANOL and VAPOL catalysts could be reduced to 1 mol % and there was no effect on the yield or asymmetric induction. Most of the reactions in Table 5 were performed with the same number of moles of the catalyst, and thus the reactions with decreased loadings were carried out by increasing the amounts of the reagents. For example, the reaction in entry 9 was performed with 11.6 g (35 mmol) of imine **21d** and 39 mg (0.09 mmol) of the VANOL ligand. With these lower catalyst loadings it was found most convenient to purify the aziridine **15d** by crystallization rather than chromatography. Except for entry 8, aziridine **15d** could be obtained in 97−98% ee by two crystallizations from methylene chloride/hexanes. In an effort to determine the overall yield and asymmetric inductions for these reactions, the aziridine remaining in the mother liquors from the two crystallizations was purified by silica gel chromatography. As can be seen from the data in the Table 5, no significant loss in yield or induction was observed for either ligand when the catalyst loading was reduced to 0.5 mol %. At 0.25 mol % loading, the reaction with the VANOL catalyst was complete but that with VAPOL only went to 80% conversion. Even at 400 turnovers, the VANOL-derived catalyst gives an 89% yield and 90% ee for aziridine **15d** (entry 9). This is the highest turnover reported for an AZ reaction of an imine. This was the limit, however, since lowering the catalyst loading to 0.1 mol % with the VANOL catalyst gave only 10% conversion in 48 h. Finally, it was demonstrated that the VAPOL ligand was recovered in 95% yield and ≥99% ee from the reaction in entry 3. This required that the crude mixture be subjected to high vacuum before crystallization to remove the excess ethyl diazoacetate. If vacuum is not applied to the crude reaction mixture, the recovery of VAPOL is only 10% and a 73% yield of the mono O−H insertion[19] product **24** was isolated, which resulted from the reaction of the ligand with excess EDA.

Acid-Mediated Deprotection. Cyclohexyl-substituted aziridine **15a** was used as a model system for the optimization of conditions for the cleavage of the dianisylmethyl from the nitrogen, with the hope that these conditions would be general for all of the aziridines **15a**−**i**. The standard conditions for the cleavage of the dianisylmethyl group from amines involve exposure to 80% HOAc at 80 °C for 5 min.[11,20] Treatment of **15a** to these conditions left the aziridine untouched. This result is consistent with the fact that aziridines are less basic than noncyclic aliphatic amines.[1f,21] This led to extensive screening of a variety of different acids[22] and the optimization of several reaction variables, which are summarized in the Supporting Information. The results of these studies produced three different sets of conditions for the deprotection of aziridines **15**.

Deprotection of eight different substituted *N*-DAM-aziridines **15** was examined under these conditions and also, for a point of comparison, hydrogenolysis condition. Specifically, these

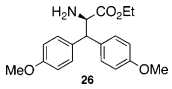
(19) For leading references, see Muthusamy, S.; Arulananda, S.; Babu, A.; Gunanathan, C. *Tetrahedron Lett.* **2002**, *43*, 3133.
(20) Hanson, R. W.; Law, H. D. *J. Chem. Soc.* **1965**, 7285.
(21) Ohwada, T.; Hirao, H.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 7486.
(22) Among the screened methods, the condition of 80% HOAc at 100 °C for 1 h resulted in only 20% conversion and the formation of a complex mixture of products, none of which was the deprotected aziridine **13a**. Treatment of **15a** with 100% HOAc at 100 °C for 0.5 h resulted in complete conversion but no detectable amount of **13a**. Other reagents such as HBr, CH_3-CHClOCOCl, and CAN gave either complex mixtures or recovered **15a**.

Table 6. Deprotection of *N*-DAM-Aziridines **15**[a]



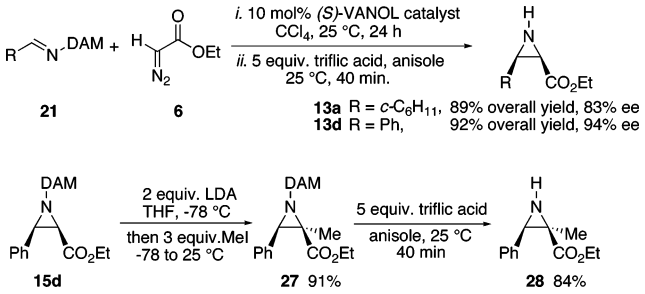
entry	series	R	method[b]	NMR yield of **13** (%)	isolated yield[c] of **13** (%)
1	a	*c*-C_6H_{11}	A	95	96
2	a	*c*-C_6H_{11}	B	95	96
3	a	*c*-C_6H_{11}	C	nd	95
4	a	*c*-C_6H_{11}	D	nd	76
5	b	*t*-Bu	A	nd	88
6	b	*t*-Bu	D	nd	75
7	d	Ph	A	97	99
8	d	Ph	B	nd	95[d]
9	d	Ph	C	nd	81
10	d	Ph	D	0	0[e]
11	e	*o*-MeC_6H_4	A	100	99
12	f	*p*-BrC_6H_4	A	98	99
13	g	*p*-$NO_2C_6H_4$	A	95	99
14	h	*p*-$OMeC_6H_4$	A	0	0[f]
15	i	1-naphthyl	A	83	72
16	i	1-naphthyl	B	94	92
17	i	1-naphthyl	C	nd	99

[a] Unless otherwise specified, all reactions were carried out with 0.5 mmol in **15** and all reactions went to completion. nd = not determined. 95−100% yield of **25** observed for methods A and B. [b] Method A: anisole solvent at 0.09 M in **15**, 5 equiv of triflic acid, 25 °C for 40 min. Method B: anisole solvent at 0.09 M in **15,** 10 equiv of trifluoroacetic acid containing 8% (by volume) H_2SO_4, 25 °C for 40 min. Method C: anisole solvent at 0.09 M in **15,** 10 equiv of H_2SO_4, 25 °C, 40 min. Method D: methanol solvent at 0.012 M in **15,** 10 mol % $Pd(OH)_2/C$, 1 atm H_2, 25 °C for 4−24 h. [c] Isolated yield after purification by silica gel chromatography. [d] Reaction was carried out on 45-mmol scale. [e] A 66% yield of **14** was isolated. [f] A 72% yield of **26** was isolated.



conditions are as follows: method A, 5 equiv of triflic acid at 25 °C for 40 min; method B, 10 equiv of trifluoroacetic acid containing 8% H_2SO_4 (by volume) at 25 °C for 40 min; method C, 10 equiv of sulfuric acid at 25 °C for 40 min; and method D, hydrogenation with Pearlman's catalyst.[13] The results of these studies are presented in Table 6 and indicate that method A gives very high yields of the deprotected aziridine **13** for most examples. 1-Naphthylaziridine **15i** was deprotected in higher yield with TFA and H_2SO_4 (method B) or with H_2SO_4 alone (method C) than with just triflic acid (method A) (Table 6, entries 15−17). The *p*-methoxyphenyl-substituted aziridine **15h** could not be deprotected without also effecting opening of the ring. Treatment of **15h** by method A led to a 72% yield of the amino ester **26** that results from acid-mediated opening of the aziridine with anisole (Table 6, entry 14). The phenyl-substituted *N*-DAM-aziridine **15d**, like the phenyl-substituted benzhydrylaziridine **7** (Scheme 3), could not be deprotected by hydrogenation with Pearlman's catalyst without also reductively opening the aziridine, where a 66% yield of **14** was isolated (Table 6, entry 10). Methods A and B are comparable for the phenylaziridine **15d**, and for this aziridine a large-scale deprotection was performed with method B, which gave a 95% yield of aziridine **13d** from 18.8 g (45 mmol) of **15d**. Methods A, B, and C give comparable results with the cyclohexyl-substituted aziridine **15a** (Table 6, entries 1−3). Hydrogenation of aziridine

Scheme 6



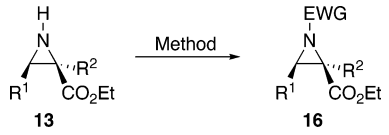
15a with Pearlman's catalyst did not give as good a yield of **13a** as did any of the other methods, and this was also true for the *tert*-butyl-substituted aziridine **15b**. It is difficult to separate the aziridine **13b** from anisole by rotary evaporator due to the volatility of this aziridine. Instead, the crude reaction mixture was loaded directly onto a silica gel column without concentration (Table 6, entry 5). The optimized methods A, B, and C are not successful with the benzhydrylaziridines **7** (Scheme 2). Complex mixtures were observed for the attempted deprotection of **7** with these methods. The absolute stereochemistry of the *N*-DAM-aziridines (2*R*,3*R*) was shown to be the same as that of aziridines produced from the corresponding reaction with benzhydrylimines. This was confirmed when it was found that the optical rotation of **13a** obtained from **15a** (99% ee) prepared with the *S*-VANOL ligand had the same sign as the optical rotation of (2*R*,3*R*)-**13a** obtained from the hydrogenolysis of (2*R*,3*R*)-*cis*-1-*N*-benzhydryl-2-carboxylethyl-3-cyclohexylaziridine **(7** in Scheme 2, R = cyclohexyl), which was in turn was prepared by the AZ reaction of the corresponding benzhydrylimine **5** with *S*-VAPOL ligand.[7b]

Generation of *N*-H-aziridines by the AZ reaction with *N*-DAM-imines and ethyl diazoacetate can be greatly simplified by cleavage of the DAM group without purification of the intermediate *N*-DAM-aziridine **15**. This one-pot process was investigated with the phenyl- and cyclohexylimines **21a** and **21d** (Scheme 6). After the aziridination reaction was finished, the crude reaction mixture was dissolved in anisole and treated with 5 equiv of triflic acid. Purification gave the *N*-H-aziridines **13a** and **13d** with the same asymmetric inductions and the same or slightly better overall yields (Tables 4 and 7). Thus purification of the *N*-DAM-aziridine becomes unnecessary. Triflic acid was also found to be effective for deprotecting the trisubstituted *N*-DAM-aziridine **27**, which gave the *N*-H-aziridine **28** in 84% yield. Trisubstituted aziridine **27** was prepared from aziridine **15d** by a highly diastereoselective alkylation. The alkylation of aziridine-2-carboxylates is a rare event, which had previously been observed only under special circumstances.[23] However, we recently reported that this process is quite general for *N*-benzhydryl-substituted aziridines, where the steric bulk of this group apparently blocks the normally predominant Claisen condensation pathway.[7d] The alkylation of **15d** reveals that this highly diastereoselective alkylation process can be extended to *N*-DAM-aziridines, and in fact it occurs in higher yield than the corresponding benzhydrylaziridine.

Formation of Activated Aziridines and Their Applications. Activation of aziridines toward ring opening is usually achieved

(23) (a) Seebach, D.; Haner, R. *Chem. Lett.* **1987**, 49. (b) Haner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta.* **1987**, *70*, 1676. (c) Alezra, V.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 651. (d) Alezra, V.; Bonin, M.; Micouin, L; Policar, C.; Husson, H.-P. *Eur. J. Org. Chem.* **2001**, 2589.

Table 7. Protection of *N*-H-Aziridines with Activating Groups



13 16

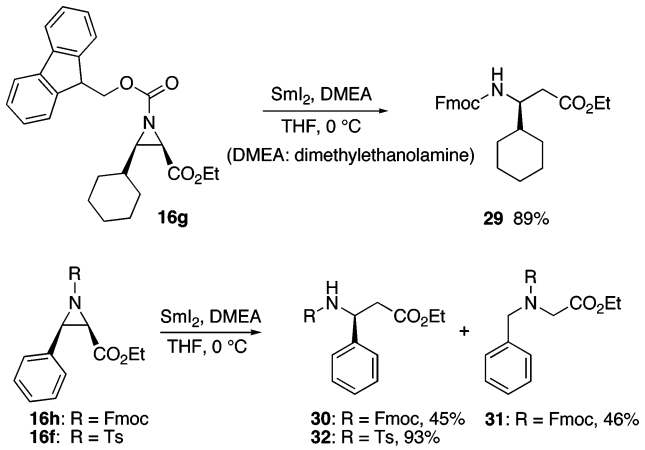
13	R^1	R^2	method[a]	EWG	16	% yield 16
13a	*c*-C_6H_{11}	H	A	Boc	**16a**	99
13d	Ph	H	A	Boc	**16b**	98
13g	*p*-$NO_2C_6H_4$	H	A	Boc	**16c**	95
13i	1-naphthyl	H	A	Boc	**16d**	98
13i	1-naphthyl	H	A	Boc	**16d**	90[b]
13a	*c*-C_6H_{11}	H	B	Ts	**16e**	100
13d	Ph	H	B	Ts	**16f**	93
13a	*c*-C_6H_{11}	H	C	Fmoc	**16g**	92
13d	Ph	H	C	Fmoc	**16h**	94
28	Ph	Me	C	Fmoc	**16i**	100

[a] Method A: 1.5 equiv of $(Boc)_2O$, 3 equiv of $NaHCO_3$, MeOH, 25 °C, ultrasound, 2 h. Method B: 1.6 equiv of TsCl, 3 equiv of Et_3N, CH_2Cl_2/$CHCl_3$ (1:1), 0 °C, 48 h. Method C: 1 equiv of 9-fluorenylmethylchloroformate, 2 equiv of $NaHCO_3$, acetone/H_2O (3:1), 25 °C, 24 h. [b] Overall yield for the two steps from **15i** cleaved with method B in Table 7.

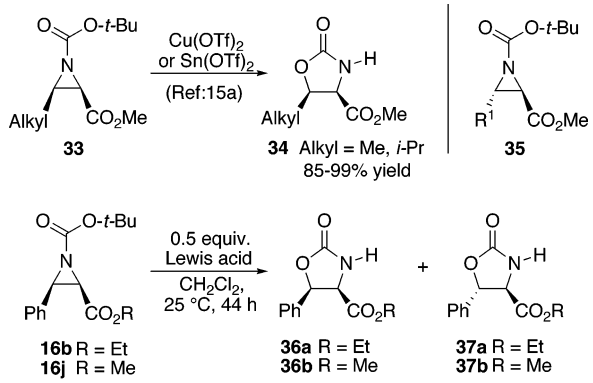
by installation of carbonyl or sulfonyl groups on the nitrogen.[1] Selected examples of *N*-H-aziridines **13** and **28** were protected with Boc, Fmoc, and tosyl groups, and the results are presented in Table 7. Of the many methods[24] for introduction of the Boc group, that involving $NaHCO_3$ in methanol with ultrasound was found to be most efficient.[24a] Thermal methods that involved triethylamine or sodium hydride gave comparable yields but the procedures were less convenient and the reaction times were longer. It was also found that it was not necessary to purify the *N*-H-aziridine prior to activation. The overall yield of Boc-aziridine **16d** from *N*-DAM-aziridine **15i** is the same whether or not the intermediate *N*-H-aziridine **13i** is purified. A check of the consequences of deprotection of *N*-DAM-aziridines and protection of *N*-H-aziridines on optical purity was performed for aziridines **15d** and **15g** and their conversion to **16b** and **16c**, and it was found that there was no erosion of the percent enantiomeric excess and no evidence for isomerization to trans isomers for the deprotection and reprotection reactions with activating groups. Introduction of the tosyl[25] and Fmoc[26] groups was achieved in excellent yields with methods B and C, respectively, as indicated in Table 7.

Reductive opening of aziridine-2-carboxylates at the C−N bond next to the carboxyl group is a very convenient method for access to β-amino esters.[27] We were interested in examining the possibility of developing the AZ reaction of imines with the VAPOL and VANOL catalysts as a direct entry to Fmoc-protected β-amino esters. Samarium diiodide has been developed as a reliable method for this type of reductive opening on a variety of aziridines, largely with *N*-Boc or *N*-tosyl activating groups on the nitrogen. Few examples have been reported for

Scheme 7



Scheme 8



R	Lewis acid	% Yield **36** + **37**	Ratio **36** : **37**
Et	BF_3•OEt_2	84	3.2 : 1
Et	$Cu(OTf)_2$	99	0.7 : 1
Me	BF_3•OEt_2	75	2.1 : 1
Me	$Cu(OTf)_2$	85	0.5 : 1

Fmoc-protected aziridines,[28] and we were thus eager to examine the first example of this reductive opening of monocyclic aziridines with a cis-2,3-disubstitution pattern. As shown in Scheme 7, reduction of the cyclohexyl-substituted aziridine **16g** with samarium diiodide gave rise to the clean formation of Fmoc-protected β-amino ester **29** in 89% yield. Reductive opening of the phenyl-substituted Fmoc-protected aziridine **16h**, on the other hand, occurred with both C−N and C−C bond cleavage to give a mixture of the α- and β-amino esters **30** and **31** in a 1:1 ratio. Clearly, the presence of the aryl group is facilitating the undesirable cleavage of the C−C bond. However, this would not restrict access to the majority of β^3-analogues of the naturally occurring β-amino acids, which have alkyl substituents on the β-position. The C−C bond cleavage could be completely avoided if the Fmoc group was replaced by the tosyl group. Reduction of the aziridine **16f** gave the β-amino ester **32** in 93% isolated yield with no detectable amount of the C−C bond cleavage product.

The Lewis acid-mediated ring expansion of *N*-Boc-aziridines to oxazolidinones is a very attractive reaction since it can occur with high yields and stereoretention at the migrating carbon with stereospecificity for cis and trans isomers.[15] Tomasini and Vecchione[15a] demonstrated that *cis*-3-alkyl-substituted aziridine-

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(26) (a) Schon, I.; Kisfaludy, L. *Synthesis* **1986**, *4*, 303. (b) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404.

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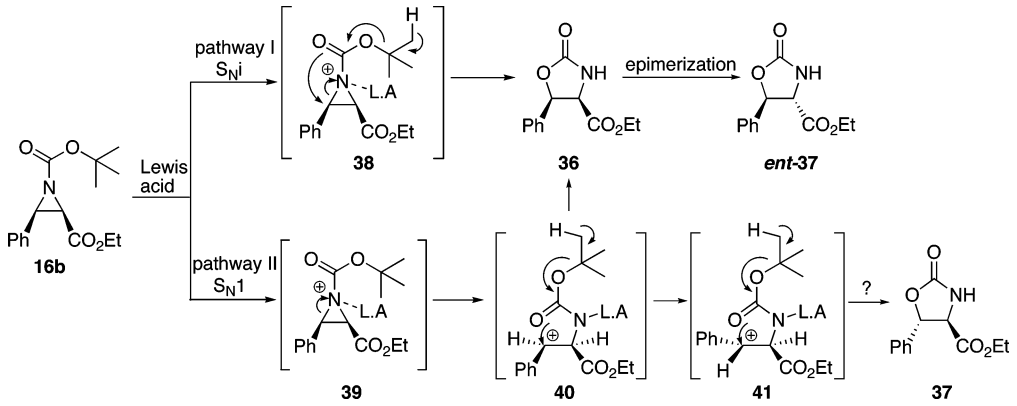
Scheme 9

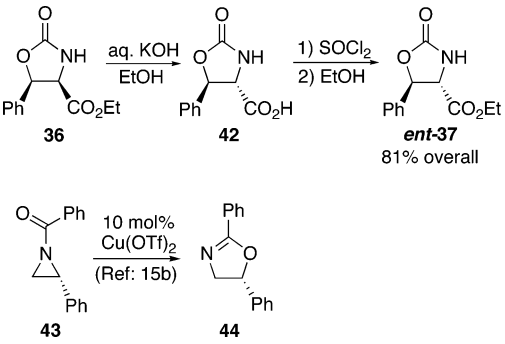


2-carboxylates of the type **33** will undergo Lewis acid-mediated ring expansion to give the oxazolidinone **34** in excellent yields and with complete retention of stereochemistry (Scheme 8). They also found the corresponding trans isomers **35** will undergo ring expansion with retention of stereochemistry to give *trans*-oxazolidinones. In the trans series **35**, this included examples where the R^1 group was both aryl and alkyl, but only reactions of alkyl derivatives were reported for the cis series **33**. To complete the series, we thus examined the reaction of ring expansion of *N*-Boc-aziridine **16b** with boron trifluoride etherate and with copper(II) triflate. To our surprise, this ring expansion was nonselective with both Lewis acids, giving good chemical yields but mixtures of *cis*- and *trans*-oxazolidinones **36** and **37**. To compare directly with the alkyl-substituted *cis*-aziridines **33**, the methyl ester **16j** was also prepared,[29] and like the ethyl ester **16b**, it gave a mixture of cis and trans isomers of the ring-expanded products.

The source of the loss of stereochemical information in the ring expansion of phenyl-substituted aziridine **16b** has two reasonable origins (Scheme 9). The first is that the ring expansion occurs with retention of configuration at the benzylic carbon in **38** via a concerted S_Ni mechanism, giving the cis-substituted oxazolidinone **36**, which is followed by an epimerization at the carbon bearing the ester group under the reaction conditions, which would lead to trans isomer *ent*-**37** (pathway I). A second is that the reaction proceeds by an S_N1 mechanism involving the benzylic cation **40** which can close on oxygen to give the cis isomer **36** or through the C−C bond rotation to give the trans isomer **37** (pathway II). These two pathways can be distinguished since they would lead to enantiomeric forms of the trans isomer **37**.

To determine which mechanism was operative, the cis isomer **36** that was isolated from the ring expansion of **16b** was treated with KOH in ethanol, which resulted in both hydrolysis and complete epimerization at the C2 position (Scheme 10).[30] Esterification of acid **42** gave the trans isomer of *ent*-**37**, which was determined to have a rotation opposite to that of the compound isolated from the ring expansion of **16b**. Thus, it can be concluded that the ring opening of **16b** proceeds by an S_N1 mechanism and that the cis and trans isomers **36** and **37**

Scheme 10



were resulted from rotation about a carbon−carbon (C2−C3) bond in the carbocation **40**. There is evidence to support both S_N1 and S_Ni mechanisms in the ring expansion of *N*-acylaziridines.[15] Lectka and co-workers[15e] have found that ring expansion of the *N*-benzoylaziridine **43** gives oxazolidine **44** with complete retention of configuration and proposed that it occurs via an S_N1 mechanism in which the carbocation undergoes closure faster than bond rotation. The difference in the present case may be attributable to the eclipsing interaction of the phenyl and ester groups in cation **40**, which leads to more rapid bond rotation. This suggests that the ring expansion of the *trans*-aziridine **35**, with R^1 equal to phenyl, also occurs via an S_N1 mechanism and that selective formation of the *trans*-oxazolidinone is just a consequence of the more stable conformation of the intermediate carbocation.

Conclusion

N-DAM-imines have been shown to be excellent substrates for the AZ reaction with ethyl diazoacetate mediated by boron catalysts derived from either the VANOL or VAPOL ligand. These reactions produced *N*-DAM-protected 3-substituted aziridinyl-2-carboxylate esters with high yields and high asymmetric inductions and also with high diastereoselectivity for the *cis*-aziridines. Up to 97% ee was observed for the aziridines, and for each substrate examined, the optical purity of the aziridine could be enhanced to >99% ee with a single crystallization. Both catalysts are highly enantioselective, and the catalyst loading can be lowered to 1 mol % with no loss in the asymmetric induction of 95% ee for the *N*-DAM-imine of benzaldehyde. With the same imine, loading of the VANOL catalyst can be lowered to 0.25 mol % and still provide the aziridine in excellent yield and with 90% ee. The VAPOL ligand can be recovered in 95% yield with no loss in optical activity.

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(30) (a) Hamersak, Z.; Sepac, D.; Ziher, D.; Sunjic, V. *Synthesis* **2003**, *3*, 375. (b) Monache, G.; Giovanni, M. C. D.; Misiti, D.; Zappia, G. *Tetrahedron: Asymmetry* **1997**, *8*, 231. (c) Tanaka, H.; Sawayama, A. M.; Wandless, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 6864.

Competition studies with the *N*-DAM-imine of benzaldehyde revealed that the catalyst derived from the VANOL ligand was twice as fast as that from the VAPOL ligand. Similar competition studies with *N*-DAM-imine shows that it reacts 3.8 times as fast as the corresponding benzhydrylimine with the VAPOL catalyst and 3.0 times faster with the VANOL catalyst. Several methods for acid cleavage of the DAM group from the aziridine were optimized and were shown to give excellent yields of the unprotected *N*-H-aziridines with a number of substrates, including both 3-aryl- and 3-alkyl-substituted aziridines. The unprotected *N*-H-aziridines could be converted to activated aziridines, which were shown to be valuable synthetic intermediates for the preparation of β-amino acids via samarium diiodide reductive opening of the aziridine ring and for the preparation of oxazolidinones via ring expansion of their N-acyl derivatives. In the case of the latter, it was shown that ring expansion of a 3-phenyl-substituted derivative occurs via an S_N1 mechanism.

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Supporting Information Available: Crystallographic details for compound **11**, procedures for the preparation of new compounds, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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