Catalytic Asymmetric Aziridination with Catalysts Derived from VAPOL and VANOL

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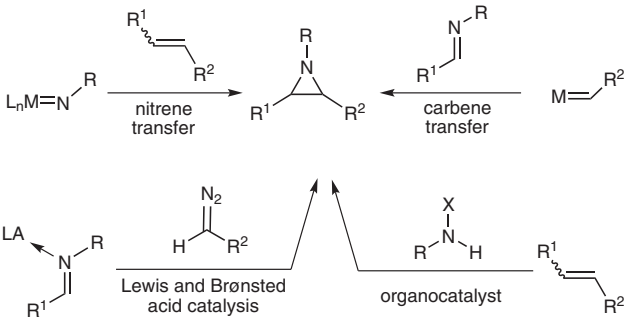
Abstract: This Account describes the discovery and development of the catalytic asymmetric aziridination reaction (AZ reaction) that has been the subject of efforts in our laboratory over the last 12 years. The optimized catalyst system involves catalysts generated from either the VAPOL or VANOL ligand and triphenyl borate. These catalysts are effective for formation of aziridines from the reaction of imines that bear a *N*-benzhydryl substituent with stabilized diazo compounds including the commercially available ethyl diazoacetate (EDA). The reaction is general for *N*-benzhydryl imines prepared from electron-rich and electron-poor aromatic aldehydes, as well as from primary, secondary and tertiary aliphatic aldehydes. This reaction is highly enantioselective and diastereoselective giving *cis*-3-substituted aziridine-2-carboxylates in excellent yields. This Account presents the scope of the AZ reaction as defined by the work that has been done in our laboratory up to the present time, as well as applications of the resulting aziridines that have been demonstrated to date.

Key words: aziridination, Lewis acids, chiral ligands, asymmetric catalysis

1 Introduction

Aziridines are strained, three-membered, saturated, nitrogen-containing heterocycles. The synthetic utility of aziridines derives in large part from the fact that they readily undergo ring-opening reactions with a variety of nucleophiles with high or often complete stereoselectivity and regioselectivity.[1] Methods for the preparation of optically pure aziridines from chiral acyclic precursors have received considerable attention;[1] in contrast, the development of catalytic asymmetric methods for the synthesis of aziridines from achiral precursors has been much more limited and has proven to be a considerably challenging undertaking.[2,3]



Scheme 1 Four approaches for catalytic AZ reactions

The catalytic asymmetric aziridination (AZ) reactions that have been developed in the past decade and a half can be classified into four approaches, which differ by how one or two new carbon–nitrogen bonds are created (Scheme 1). The first catalytic AZ reaction involved transfer of a nitrene from a metal nitrene to an olefin and was reported in the same year by Evans,[4a] Jacobsen[4b] and Katsuki,[4c] and their co-workers. Attempts to improve on the metal nitrene approach have lead to a series of ligand modifications which culminated in recent reports by Katsuki and co-workers[4d,e] that a highly modified salen ligand can provide high asymmetric inductions (85–99% ee) with a number of vinylarenes. Aliphatic alkenes also gave good inductions[4d,e] but with low yields and, thus, the development of a catalyst with a broader scope of alkene substrates remains an actively pursued goal. A second and complementary approach involves the asymmetric transfer of a carbene from a metal carbene to an imine.[5] The only real success with this approach involves a cleverly designed double catalytic cycle developed by Aggarwal and co-workers that includes the transfer of a carbene from a metal carbene to a chiral sulfide giving a chiral sulfur ylide, which in turns transfers the carbene to an imine.[5a–e] High asymmetric inductions could be obtained with this method. The drawbacks of this approach are that only modest control of the *cis*/*trans* selectivity of the aziridines could be achieved and that 20 mol% of the chiral sulfide is required. The third approach involves the organocatalytic-mediated addition of a nitrene surrogate to activated olefins (α,β-unsaturated carbonyl compounds) and

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asymmetric versions of this reaction have just recently appeared.[6] The final approach involves the activation of an imine by a chiral Lewis or Brønsted acid toward reaction with a diazo compound. It is this latter approach that has been the focus of studies in our laboratory. The purpose of this Account is to tell the story of how the catalytic AZ reaction of imines with ethyl diazoacetate (EDA) with catalysts derived from triphenyl borate and the VANOL or VAPOL ligand developed in our laboratory over the last 12 years.[7]

2 Asymmetric Aziridination of Ethyl Diazoacetate with Imines

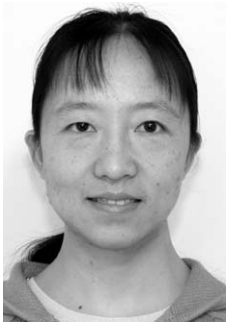
2.1 Discovery of the Original Catalytic System

Our study of the catalytic AZ reaction started in the late 1990s, and was inspired by the pioneering studies of Brookhart and Templeton[8] and of Jørgensen[7a,b,9] and their co-workers who reported on the fact that simple nonchiral Lewis acid such as $BF_3{\cdot}OEt_2$ and $Yb(OTf)_3$ could catalyze the formation of aziridines from imines and EDA (Scheme 2). The mechanism proposed involves the coordination of the Lewis acid to the imine, which activates it toward attack by the diazo compound leading to the formation of the zwitterion **7**. Rotation about the newly formed carbon–carbon bond converts conformer **7a** into **7b** and then backside displacement of nitrogen by the original imine nitrogen leads to the formation of the *cis*-aziridine **3**. The enamine side products **4** and **5** can be accounted for by either a 1,2-hydride or 1,2-aryl shift accompanied by nitrogen loss in zwitterion conformers **7c** and **7d**, respectively, followed by tautomerization.

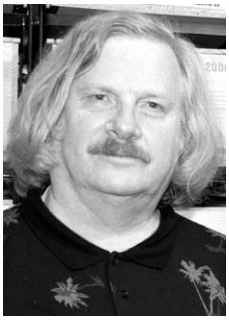
Prior to the reports by Brookhart and Templeton[8] and by Jørgensen[7a,b,9] and their co-workers, we had shown that effective chiral Lewis acids could be generated from the vaulted biaryl ligands VANOL and VAPOL (Figure 1).[10] The design and synthesis of these ligands was inspired by the tremendous success associated with BINOL (**10**).[11] One of the limitations of BINOL is that the bulk of the space that is asymmetrically discriminated is on the oppo-

Biographical Sketches

Yu Zhang carried out his undergraduate research at East China University of Science and Technology in Shanghai, China. He received his B.S. degree in chemistry in 1996 and then, in 2000, he joined Professor William D. Wulff's group as a graduate student at Michigan State University, USA. He obtained his Ph.D. degree in 2006 after working in the area of mechanism and methodology development of catalytic asymmetric aziridination. He is currently a postdoctoral scholar at the University of Wisconsin–Madison, working with Professor Richard P. Hsung in the area of ynamide chemistry and natural products synthesis.



Zhenjie Lu obtained her B.S. degree in chemistry in 1996 from East China University of Science and Technology in Shanghai, China. She started as a graduate student at Michigan State University, USA under Professor William D. Wulff's direction in 2002, and finished her Ph.D. degree in 2008. Her research involves studies on the optimization and synthetic applications of catalytic asymmetric aziridination reactions.



William D. Wulff grew up on a dairy farm in northern Wisconsin, USA (near Wulff Valley). He was an undergraduate student at the University of Wisconsin–Eau Claire. In 1974 he joined Professor Thomas Barton's group for his graduate studies at Iowa State University and worked in the area of organosilicon reactive intermediates; he received his Ph.D. degree in 1979. In the same year he joined Professor Martin Semmelhack at Princeton University as an NIH postdoctoral fellow and subsequently he joined the Chemistry Faculty at the University of Chicago in 1980 as an assistant professor. He was promoted to professor of chemistry in 1992. In 1999 he moved to Michigan State University where he is currently professor of chemistry. His research program has focused on synthetic methods and synthetic applications of Fischer carbene complexes and on catalytic asymmetric synthesis.

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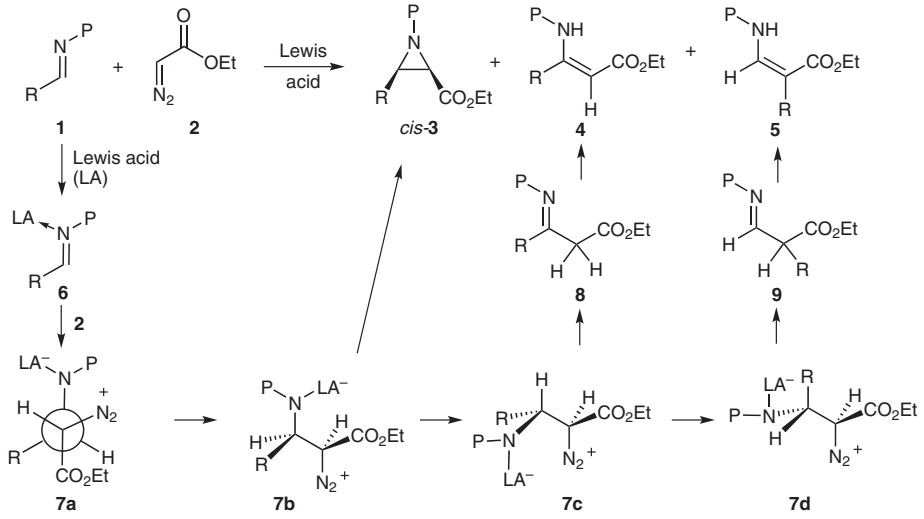
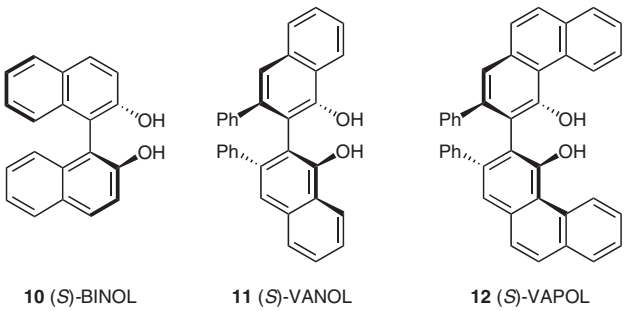


Scheme 2 The Lewis acid catalyzed AZ reaction

site side of the chiral axis from the hydroxy groups and thus presumably from where the reaction takes place. Our simple idea was to move the phenyl rings distal to the hydroxy groups in BINOL to a position proximal to the hydroxy groups in such a way as to produce the 2,2′-binaphthol **11** (VANOL). The resultant anticipation was that there would be a more pronounced chiral pocket for VANOL than for BINOL. If this was a good idea, then adding an extra phenyl group to extend the chiral pocket as indicated in the 3,3′-biphenanthrol **12** (VAPOL) would be even better and this ligand would be expected to give higher asymmetric inductions than either VANOL or BINOL. This analysis was vindicated in our early studies on catalytic asymmetric Diels–Alder reactions where it was found that a catalyst prepared from diethylaluminum chloride and VAPOL is superior to the corresponding catalysts prepared from either VANOL or BINOL.[12] It has been generally true that of the various catalyst systems we and others have examined,[12,13] catalysts prepared from VAPOL are superior to those prepared from VANOL or BINOL, with the exception being the Baeyer–Villiger reaction where the VANOL catalyst gave the highest inductions.[13b]

Given our prior success with the chiral Lewis acid derived from diethylaluminum chloride and the VAPOL ligand in the Diels–Alder reaction of cyclopentadiene and methacrolein,[12a] and given the fact that nonchiral Lewis acids could catalyze the formation of aziridines from imines and EDA,[7a,b,8,9] we pursued the possibility of a catalytic AZ reaction with chiral Lewis acids prepared from VAPOL. The first reaction screened was of *N*-benzylideneaniline with EDA (**2**) using a catalyst generated from VAPOL and diethylaluminum chloride (Table 1, entry 1). Despite the low yield and significant amounts of enamine side products **4** and **5**, the *cis*/*trans* ratio was encouraging. The asymmetric induction was 25% ee and could be increased to 32% ee by lowering the temperature to 0 °C (not shown), while at –40 °C the reaction came to a stop.[14] Despite these low asymmetric inductions, at the time they were comparable to those of Jacobsen's copper-catalyzed EDA addition to imines[15] and higher than that reported by Rasmussen and Jørgensen for the same reaction with a variety of different chiral Lewis acids.[7a] We had also previously observed that both the VANOL and VAPOL catalysts derived from $BH_2Br{\cdot}SMe_2$ gave excellent asymmetric inductions in the Diels–Alder reaction of cyclopentadiene and methacrolein. Indeed, a significant increase in induction from 25% ee to 59% ee was observed for VAPOL when $BH_2Br{\cdot}SMe_2$ was used as the Lewis acid (Table 1, entry 1 vs entry 3). This change in Lewis acid also resulted in a dramatic increase in the rate of the reaction since it went to completion with 10 mol% catalyst in 2 minutes (Table 1, entry 4). Interestingly, lowering the temperature to 0 °C lead to a decrease in induction (Table 1, entry 5). Finally, various nitrogen protecting groups on the imine were then examined in the hope of enhancing the selectivity of the reaction. The *o*-hydroxyphenyl-substituted imine, and the benzyl- and trityl-protected imines all gave low turnover, while the benzhydryl-protected imine gave the highest induction (78% ee) and highest yield of any of the catalyst systems (Table 1) despite the fact that the reaction only went to 50% conversion, and remarkably, the yield of the enamine side products dropped to less than significant levels (Table 1, entry 9).



10 (*S*)-BINOL **11** (*S*)-VANOL **12** (*S*)-VAPOL

Figure 1 BINOL, VANOL and VAPOL ligands

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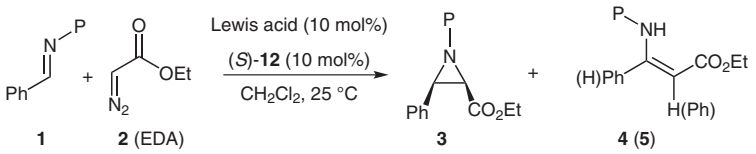
Table 1 Initial Development of the AZ Reaction System[a]



1 2 (EDA) 3 4 (5)

Entry	P	Lewis acid	Time (h)	Yield[b] (%) of **3**	ee (%) of **3**	Ratio[c] *cis*/*trans*-**3**	Yield[c] (%) of **4** + **5**
1	Ph	Et_2AlCl	20	(50)	25	>19:1	41
2	Ph	$BH_2Cl{\cdot}SMe_2$	24	10	24	>19:1	40
3	Ph	$BH_2Br{\cdot}SMe_2$	4	40	59	>19:1	44
4	Ph	$BH_2Br{\cdot}SMe_2$	0.03	35	58	>19:1	40
5[d]	Ph	$BH_2Br{\cdot}SMe_2$	20	35	40	>19:1	30
6	2-HOC_6H_4	$BH_2Br{\cdot}SMe_2$	24	(20)	n.d.[e]	>19:1	<5
7	Bn	$BH_2Br{\cdot}SMe_2$	20	(10)	n.d.[e]	6:1	<5
8	Tr	$BH_2Br{\cdot}SMe_2$	24	(0)	n.d.[e]	n.d.[e]	n.d.[e]
9	$CHPh_2$	$BH_2Br{\cdot}SMe_2$	4	(51)	78	18:1	<5
10[f]	$CHPh_2$	$BH_2Br{\cdot}SMe_2$	24	64	88	12:1	19

[a] Unless otherwise specified, all reactions were performed at 0.1 M in imine **1** with 1.04 equivalents of EDA (**2**). The catalyst was prepared by reacting (*S*)-VAPOL (**12**) with Lewis acid at 25 °C for 30 min.
[b] Isolated yield. Yields in parenthesis were determined from the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Determined from the ^{1}H NMR spectrum of the crude reaction mixture.
[d] Reaction at 0 °C.
[e] n.d. = not determined.
[f] Catalyst prepared by heating a CH_2Cl_2 soln of (*S*)-VAPOL (**12**) with $BH_2Br{\cdot}SMe_2$ (3 equiv) at 50 °C for 2 h, and then exposure to 0.1 mmHg at 50 °C for 0.5 h.

Upon the discovery of its superior reactivity and selectivity, the *N*-benzhydryl imine quickly became the focus of further optimization. At the same time it was found that the reactions with catalysts generated from $BH_2Br{\cdot}SMe_2$ were not reproducible and it was first suspected to be related to incomplete catalyst formation. The original procedure for catalyst preparation involved the reaction of the VAPOL ligand with 1 equivalent of $BH_2Br{\cdot}SMe_2$ at room temperature for 30 minutes. After a series of experiments, an optimized procedure was identified which involved heating 1 equivalent of the chiral ligand with 3 equivalents of the boron species at 50 °C for 2 hours, followed by exposure to a high vacuum (0.1 mmHg) at 50 °C for 0.5 hour to remove the volatile species. With this new procedure the reaction was still not reproducible with the % ee ranging from 60% to 90% ee. Nonetheless, the upper end of the induction was improved to 88% ee (Table 1, entry 10).

Continued study of catalysts prepared from (*S*)-VAPOL and $BH_2Br{\cdot}SMe_2$ revealed that there were inconsistencies between different batches of $BH_2Br{\cdot}SMe_2$. Figure 2 presents the ^{1}H NMR spectrum of a sample of $BH_2Br{\cdot}SMe_2$ that was purchased from Aldrich Chemical Co. and reveals the presence of four boron compounds as their dimethyl sulfide complexes. Upon integration of the methyl groups from each of the dimethyl sulfide complexes, it

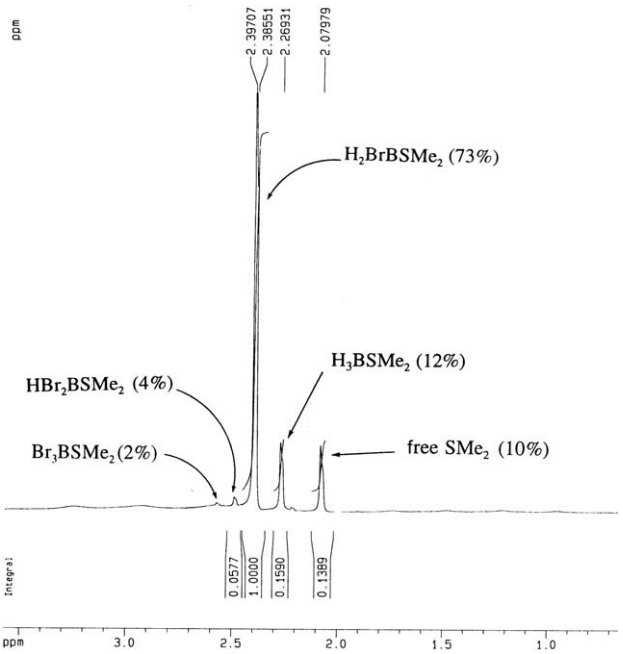


Figure 2 ^{1}H NMR spectrum of a sample of $BH_2Br{\cdot}SMe_2$ purchased from Aldrich Chemical Co.

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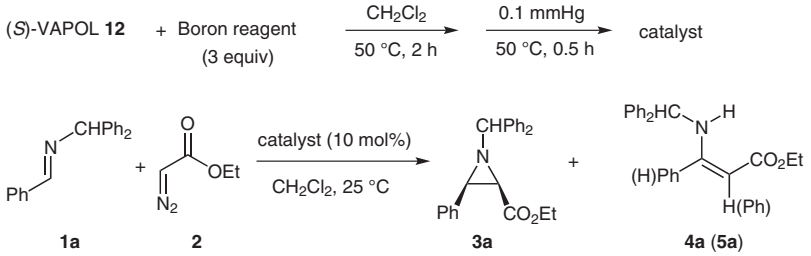
was found that for this particular sample $BH_2Br{\cdot}SMe_2$ comprised only 73% of the mixture. The other components were identified as $BHBr_2{\cdot}SMe_2$ (4%), $BBr_3{\cdot}SMe_2$ (2%), $BH_3{\cdot}SMe_2$ (12%) and free dimethyl sulfide (10%).[16] Thus, it became clear that to avoid reproducibility problems, it would be necessary to purify the $BH_2Br{\cdot}SMe_2$.

The preparation of $BH_2Br{\cdot}SMe_2$ has been reported by Brown and Ravindran;[16] we repeated this procedure and found that the purity could be further enhanced to >98% by distillation.[14] We were quite surprised to find that the catalyst prepared from purified $BH_2Br{\cdot}SMe_2$ only gave 66% ee for the formation of the aziridine **3a** (Table 2, entry 1). With this result we were forced to consider the possibility that one of the minor boron species generated a more selective catalyst and that a high reactivity compensated for its low abundance. If this was the case, it was considered likely that such a highly active catalyst would be produced from a stronger Lewis acid than $BH_2Br{\cdot}SMe_2$. Thus, catalysts were generated from $BHBr_2{\cdot}SMe_2$ and $BBr_3{\cdot}SMe_2$ but these aziridinations only lead to **3a** with 75% and 32% ee, respectively (Table 2, entries 2 and 3). The only boron species remaining that was not examined was $BH_3{\cdot}SMe_2$ and this was put off to the end since it was not considered likely to produce a catalyst with high reactivity. Nonetheless, when this boron species was evaluated, it was found to give the aziridine **3a** in 93% ee (Table 2, entry 4). A more active catalyst was obtained when $BH_3{\cdot}THF$ was used as the boron source, and the resulting catalyst gave **3a** in 74% yield and 97% ee (Table 2, entry 5).

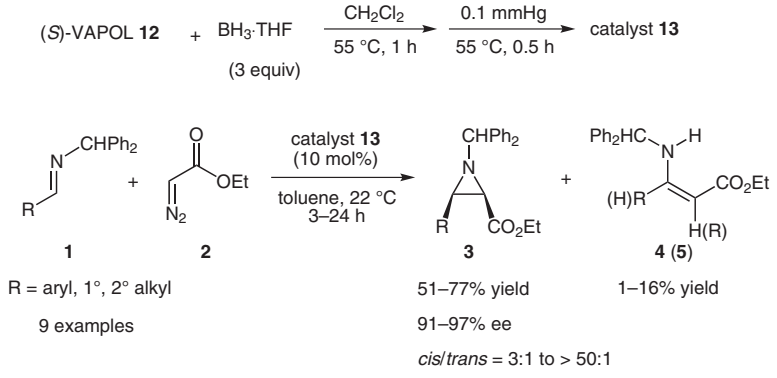
With the success of the catalyst generated from $BH_3{\cdot}THF$, the scope of the reaction was examined with a series of nine different imines and, as indicated in Scheme 3, the *N*-benzhydrylaziridines **3** were obtained in moderate to good yields with 91–97% ee and with *cis*/*trans* selectivities of 3:1 to >50:1; these results constituted our first report on the AZ reaction with the VAPOL ligand.[17]

While the catalyst prepared from $BH_3{\cdot}THF$ and (*S*)-VAPOL was quite effective in the catalytic AZ reactions of *N*-benzhydryl imines with EDA, over time it was realized that there was some variability in the asymmetric induction. In fact, the induction was found to vary with the batch of $BH_3{\cdot}THF$, which was used as purchased from Aldrich Chemical Co. as a 1 M solution in tetrahydrofuran. Analysis by ^1H NMR spectroscopy revealed the presence of a mixture of species in the bottle of $BH_3{\cdot}THF$, and one was identified as tributyl borate with the aid of an au-

Table 2 AZ Reaction Catalyzed by VAPOL–Boron Species



Entry	Boron reagent	Time (h)	Conversion (%)	Yield (%) of **3a**	Ratio *cis*/*trans*-**3a**	ee (%) of **3a**	Yield (%) of **4a** + **5a**
1	$BH_2Br{\cdot}SMe_2$	20	100	53	>50:1	66	19
2	$BHBr_2{\cdot}SMe_2$	11	100	51	>50:1	75	24
3	$BBr_3{\cdot}SMe_2$	24	80	33	12:1	32	28
4	$BH_3{\cdot}SMe_2$	48	50	30	>50:1	93	6
5	$BH_3{\cdot}THF$	3	100	74	>50:1	97	2.4



Scheme 3 Catalytic AZ reaction with catalyst derived from $BH_3{\cdot}THF$

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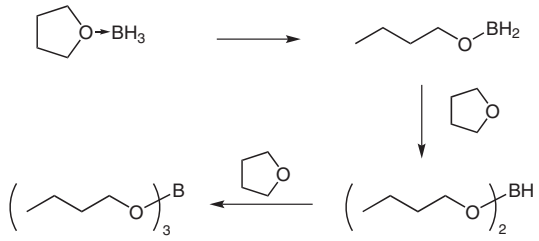
thentic sample. It is known that BH_3·THF will thermally decompose to give dibutoxyborane and tributyl borate and this presumably occurs via reductive ring opening of the tetrahydrofuran ring, as indicated in Scheme 4. A recent study revealed that a 1 M solution of BH_3·THF in tetrahydrofuran will be completely converted into tributyl borate (>90%) at 50 °C in 118 hours.[18] The catalyst prepared in Scheme 3 is made by heating a solution of BH_3·THF and (*S*)-VAPOL in a solvent that is a mixture of dichloromethane and tetrahydrofuran and which is predominately dichloromethane. Presumably, there is a mixture of boron species present in this catalyst. The process shown in Scheme 4 can also occur as BH_3·THF is being stored in the refrigerator. One particularly old bottle of BH_3·THF was found to be nearly pure tributyl borate by ^{1}H NMR spectroscopy. In contrast, a newly purchased bottle of BH_3·THF is typically found to contain less than 2% tributyl borate.

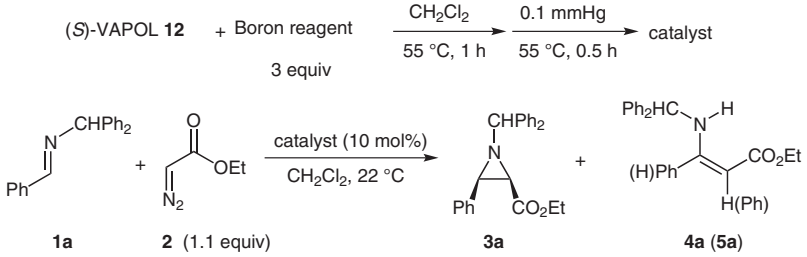


Scheme 4 Thermal decomposition of BH_3·THF

Rather than attempting to find the optimal ratio of the species shown in Scheme 4 for catalyst formation, it was decided to screen commercially available borate esters for their ability to provide effective catalysts for the AZ reaction. As a control, a newly purchased bottle of BH_3·THF was found to contain less than 2% tributyl borate, and the catalyst generated from it gave the aziridine **3a** in 89% ee (Table 3, entry 1). Obviously, it is possible that some tributyl borate or mixed butoxyboron hydrides could have been formed during catalyst generation, however, this is not consistent with the observation that a slightly higher induction was observed when the catalyst formation was performed at 0 °C (Table 3, entry 2). As can be seen from Table 3, all of the borate esters that were screened gave higher asymmetric induction than BH_3·THF, with the highest selectivity observed for triisopropyl borate; however, the catalyst from the latter species produced a very sluggish reaction that only went to 41% conversion in 92 hours (Table 3, entry 6). The optimal borate ester proved to be triphenyl borate as its catalyst derived from VAPOL gave the highest yield and *cis*/*trans* selectivity with an excellent induction of 95% ee (Table 3, entry 7).

In addition to its better selectivity profile in the catalytic AZ reaction, triphenyl borate is a more desirable precatalyst than tributyl borate since it is a solid and is thus easier to handle. In addition, its hydrolysis product is phenol and this compound was found not to inhibit the reaction. If 10 mol% phenol is added to the reaction indicated in entry 7 of Table 3, the reaction still goes to 100% completion and

Table 3 AZ Reaction Catalyzed by VAPOL–Boron Species[a]



Entry	Boron reagent	Time (h)	Conversion[b] (%)	Yield[c] (%) of **3a**	Ratio[b] *cis*/*trans*-**3a**	ee (%) of **3a**	Yield[b] (%) of **4a** + **5a**
1	BH_3·THF[d]	20	100	53	26:1	89	17
2	BH_3·THF[d,e]	3	100	58	21:1	91	20
3	$B(OMe)_3$	20	92	74	35:1	91	6
4	$B(OEt)_3$	20	67	51	30:1	92	5
5	$B(OBu)_3$[f]	10	100	72	44:1	96	5
6	$B(O\textit{i}\text{-}Pr)_3$[g]	92	41	20	>50:1	97	2
7	$B(OPh)_3$	1	100	81	>50:1	95	6

[a] Reaction performed at 0.5 M in imine **1a**.
[b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Isolated yield of *cis*-**3a**.
[d] Contains ≤2% $B(OBu)_3$.
[e] Catalyst formed at 0 °C for 24 h.
[f] 5 mol% catalyst used.
[g] Catalyst prepared with 1 equivalent of $B(O\text{-}\textit{i}\text{-}Pr)_3$.

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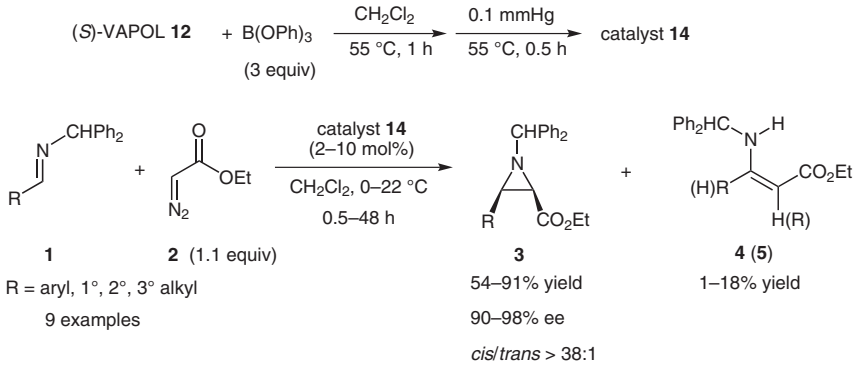


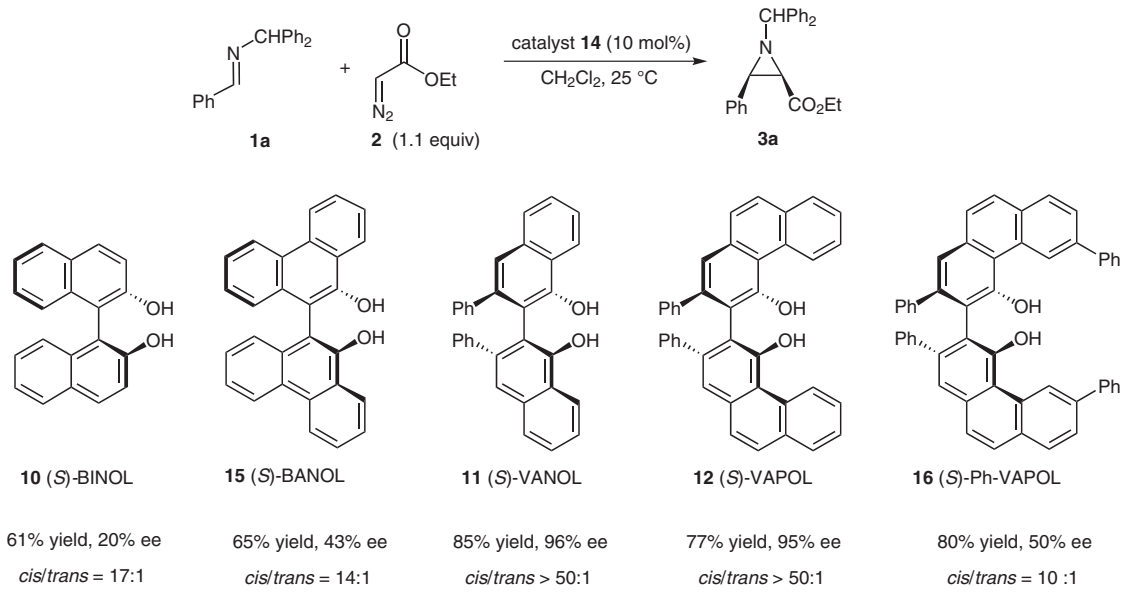
Scheme 5 Catalytic AZ reaction with catalyst derived from triphenyl borate

the results are unaffected. Thus, this leads to more consistent results over the lifetime of a purchased sample of triphenyl borate. In contrast, the addition of 10 mol% ethanol to the reaction indicated in entry 7 of Table 3 leads to an inhibition of the reaction, which only goes to 40% completion, and as a result the yield drops to 36% but the ee and *cis*/*trans* selectivity are unaffected.

A survey of nine different imines was conducted with the catalyst prepared from triphenyl borate and (*S*)-VAPOL, and these results which are summarized in Scheme 5 were published in 2000.[19] The imines **1** were prepared in a single step from benzhydrylamine and the appropriate aldehyde. All imines were purified by crystallization prior to the AZ reaction with the exception of the imine with R = *n*-propyl which was an oil and was used without purification. The catalyst prepared from triphenyl borate had a little broader scope than the catalyst derived from BH_3·THF (see Scheme 3) since it could be extended to more hindered imines bearing tertiary alkyl groups. In addition, the chemical yields and the *cis*/*trans* selectivities were slightly higher for the catalyst derived from triphenyl borate, although the inductions were about the same.

The screen with the triphenyl borate catalyst also included several different biaryl ligands, as indicated in Scheme 6.[20] BINOL did not produce a particularly effective catalyst giving aziridine **3a** in 61% yield and 20% ee. Interestingly, the BANOL ligand **15** is a 2,2′-binaphthol ligand like VANOL and yet it gave a much lower asymmetric induction than VANOL (43% ee vs 96% ee). In addition, we found that the BANOL ligand is difficult to work with and is prone to epimerization and/or decomposition. It might have been anticipated that the 6,6′-diphenyl-substituted VAPOL derivative **16**[12d] would have given a much higher asymmetric induction than VAPOL but instead it gave a dramatically reduced induction (50% ee vs 95% ee). Remarkably, VAPOL and VANOL not only gave nearly the same asymmetric induction for imine **1a** (Scheme 6) but also for all imine substrates tested to date (see Scheme 10).

We have not seen this before for other catalytic asymmetric reactions, where normally either VAPOL or VANOL is superior. It is usually the case that VAPOL gives higher asymmetric inductions than VANOL.[12,13] The only exception is the Baeyer–Villiger reaction involving an alumi-



Scheme 6 Effect of the ligand on catalyst **14** prepared from triphenyl borate

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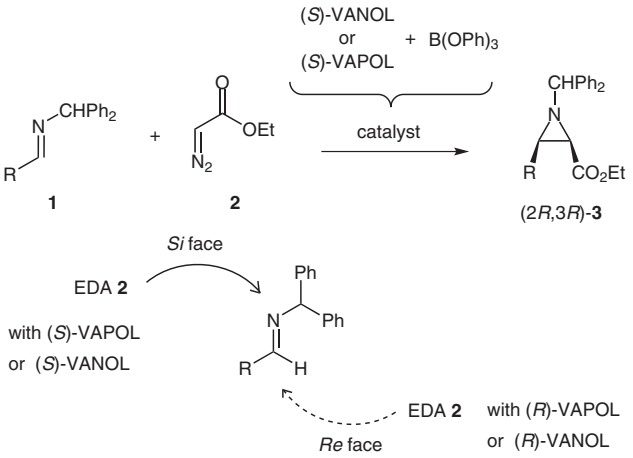
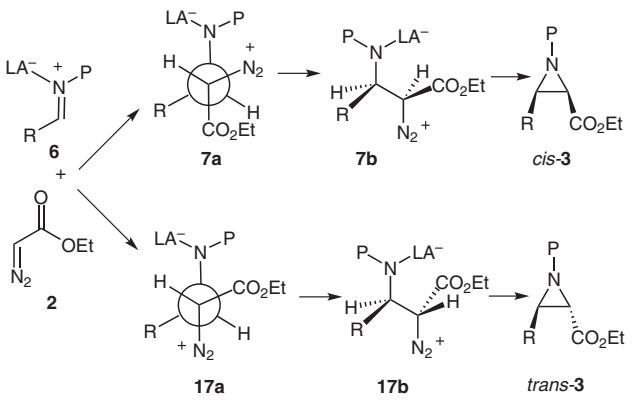
num catalyst which is optimal with the VANOL ligand.[13b] Very recently, Bergman, Ellman and co-workers have found that phosphoramidites of VAPOL and VANOL give nearly identical asymmetric inductions in the hydroarylation of alkenes,[13i] and Antilla and co-workers have found that similar inductions are observed for phosphoric acid derivatives of VAPOL and VANOL for desymmetrization of *meso*-aziridines.[13e] In addition, Lou and Schaus have found that both ligands give nearly equal inductions as catalysts in the Petasis reaction.[13h]

The catalysts derived from triphenyl borate and the *S*-enantiomers of VANOL and VAPOL both give the 2*R*,3*R*-enantiomers of aziridine **3** which results from the addition of EDA to the *Si* face of the imine **1**. This assignment was confirmed by chemical correlation in a number of examples, which are covered in the section on synthetic applications of the AZ reaction (see Section 3.4). In fact, the *S*-enantiomers of all of the ligands shown in Scheme 6 give *Si*-face addition to imine **1** in the AZ reaction, including (*S*)-BINOL. The mnemonic device for predicting the stereochemical outcome is shown in Scheme 7 and is quite simple: *S*-ligands give *Si*-face addition and *R*-ligands give *Re*-face addition.

The origin of the *cis* selectivity has not been definitively identified nor has the mechanistic pathway by which aziridines are formed from the Lewis or Brønsted acid mediated reaction of imines and diazo compounds. A number of reports have included mechanistic speculation on the pathway to aziridine formation and they all have in common the zwitterion **7** shown in Scheme 2.[7a,8,21] If this is true, then the fact that *cis*-aziridines are formed from the reaction requires that the zwitterion **7** be generated in preference to the diastereomeric zwitterion **17** (Scheme 8). Subsequent rotation about the newly formed carbon–carbon bond in **7a** and backside displacement of molecular nitrogen by the original imine nitrogen would give the *cis*-aziridine **3**. The preference for **7** over **17** may be attributed to the favorability of the interaction between the newly forming opposite charges in the transition state.[21c,d]



Scheme 7 Mnemonic for predicting the absolute stereochemistry of the AZ reaction



Scheme 8 Origin of the *cis* selectivity in the AZ reaction

2.2 Optimized Catalytic Asymmetric Aziridination System

Triphenyl borate is not a particularly strong Lewis acid, and it is not expected to promote the reaction of EDA and *N*-benzhydryl imines as readily as other stronger Lewis acids.[22] This expectation was borne out by the data in Table 4 for the reaction of the 1-naphthyl-substituted imine **1b** with EDA. Nonetheless, triphenyl borate can promote the reaction to some extent, but not as well as $BF_3{\cdot}OEt_2$ or $Yb(OTf)_3$ (Table 4, entries 1–3).[23] The best catalyst for this reaction was that generated from either VANOL or VAPOL and triphenyl borate (Table 4, entries 5 and 6). The VANOL– and VAPOL–triphenyl borate catalyst complex gave lowest amounts of the enamine side products, as well as the highest yield of the aziridine product **3b** and the highest *cis*/*trans* selectivity. This was true also for racemic VAPOL (Table 4, entry 4), which was in fact used as a general method for the preparation of racemic aziridines to aid in the analysis of the asymmetric induction with optically pure ligands.

The optimal catalyst for the AZ reaction was empirically found to result from the reaction of either the VANOL or VAPOL ligand with 3 equivalents of triphenyl borate, as outlined in Scheme 5. In the absence of any information about the structure of the catalyst, it was assumed early on that a 1:1 adduct of VAPOL and triphenyl borate was the active catalyst and that the excess 2 equivalents of triphenyl borate served to drive the formation of the catalyst to completion. Triphenyl borate has a high boiling point and will not be removed from the catalyst during the catalyst preparation protocol that involves removing the volatiles at 55 °C under high vacuum (0.1 mmHg) (see Scheme 5). Therefore, the data in Table 4 suggest that triphenyl borate could provide some background reaction and thus excess triphenyl borate could be detrimental to the asymmetric induction. To test for this, a series of experiments was performed in which the *p*-bromophenyl-substituted imine **1c** was reacted with EDA with increasing amounts of triphenyl borate; the results are shown in Table 5. Remarkably, the asymmetric induction does not begin to drop until 30 equivalents of triphenyl borate are added rel-

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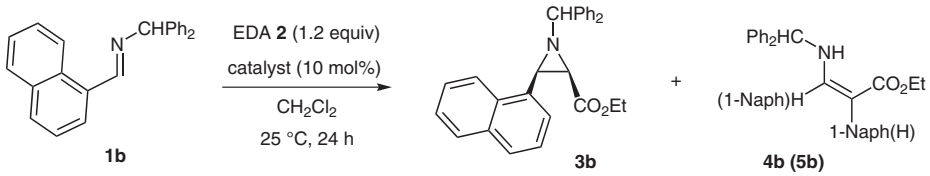
Table 4 Effect of Different Lewis Acids on the AZ Reaction



1b 3b 4b (5b)

Entry	Catalyst	Conversion[a] (%)	Yield[b] (%) of **3b**	Ratio[a] *cis*/*trans*-**3b**	ee (%) of **3b**	Yield[a] (%) of **4b** + **5b**
1	$BF_3{\cdot}OEt_2$	100	43	25:1	–	16
2	$Yb(OTf)_3$	85	39	25:1	–	14
3	$B(OPh)_3$	20	15	30:1	–	5
4	*rac*-VAPOL catalyst **14**[c]	100	88	33:1	–	4
5	(*S*)-VAPOL catalyst **14**[c]	100	87	>30:1	92	8
6	(*S*)-VANOL catalyst **14**[c]	100	85	>30:1	88	5

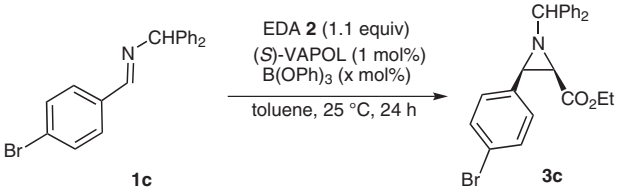
[a] Determined from the ^1H NMR spectrum of the crude reaction mixture.
[b] Isolated yield.
[c] Prepared as shown in Scheme 5.

ative to VAPOL (Table 5, entry 7). This suggests that very little background reaction is occurring under the standard conditions where 3 equivalents of triphenyl borate are employed. This is also consistent with the catalyst loading studies (*vide infra*).

The effect of solvent on the reaction of imine **1a** and EDA is shown in Table 6. Acetonitrile negatively effects the reaction, giving a lower yield of the aziridine **3a** and dramatically reduced asymmetric induction, and is the only solvent in which the reaction does not go to completion in 24 hours. The results in acetonitrile are not surprising since this solvent is envisioned to involve a Lewis acid catalyst. In this regard, it was unexpected to find that tetrahydrofuran gives essentially the same results as dichloromethane and toluene. The differences between dichloromethane (89% ee), toluene (91% ee) and carbon tetrachloride (93% ee) are small but reproducible.

Although there are variations in the inductions that can result from impurities in the starting materials and from the

Table 5 Effect of Excess Triphenyl Borate on the AZ Reaction

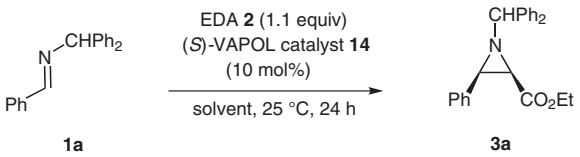


1c 3c

Entry	$B(OPh)_3$[a] (mol%)	Conversion (%)	Yield[b] (%) of **3c**	ee (%) of **3c**
1	1.5	26	25	83
2	2	98	82	85
3	2.5	97	82	88
4	3	100	85	88
5	5	100	85	89
6	10	100	85	87
7	30	100	84	83
8	3 (0% VAPOL)	26	–	–

[a] Catalyst prepared as indicated in Scheme 5, except that toluene was the solvent. The temperature was 80 °C and the amount of $B(OPh)_3$ is indicated in the table.
[b] Isolated yield.

Table 6 Solvent Effects on the AZ Reaction



1a 3a

Entry[a]	Solvent	Yield[b] (%) of **3a**	ee (%) of **3a**
1	MeCN	60[c]	26
2	THF	79	90
3	CS_2	73	91
4	benzene	83	92
5	toluene	83	91
6	$F_3CC_6H_5$	82	90
7	CH_2Cl_2	83	89
8	$CHCl_3$	81	90
9	CCl_4	84	93

[a] Catalyst prepared as indicated in Scheme 5.
[b] Isolated yield.
[c] 77% conversion.

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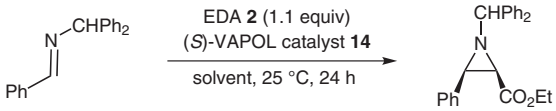
procedure by which the catalyst is made (*vide infra*), the reaction of **1a** with **2** in dichloromethane, toluene and carbon tetrachloride has been investigated under identical conditions at least a half-dozen times and the data in Table 6 represent the averages for these three solvents. The data for the other solvents in Table 6 represent only one or two runs.

The catalyst loading study shown in Table 7 was undertaken to estimate the number of turnovers that could be achieved with the VAPOL–triphenyl borate catalyst. Since the concentration of the catalyst can only be assumed to be equal to that of VAPOL, the determination of the turnovers can only be estimated. In dichloromethane the reaction of imine **1a** with EDA (**2**) will go to completion with 0.5 mol% catalyst **14** at room temperature in 24 hours at 0.1 M in imine (Table 7, entry 3). This reveals that the reaction is capable of 200 turnovers and a turnover frequency of about 8.3 h^{-1}. This is to be compared to the result with triphenyl borate (Table 4, entry 3) which shows that the reaction with this Lewis acid goes to 20% completion in 24 hours with 10 mol% catalyst, which is 0.11 turnovers·h^{-1}. While we do not know the concentration of the catalyst and thus have not yet measured k_{cat} for these reactions, these estimated turnover frequencies suggest that the VAPOL–triphenyl borate catalyst is at least 75 times faster than triphenyl borate, suggesting that the background reaction with triphenyl borate should not be significant. The data in Table 5 suggest that the relative rates should even be higher. Lowering the amount of catalyst to 0.25 mol% results in incomplete conversion (44%) in 24 hours (Table 7, entry 4). Slightly higher turnover numbers can be achieved in carbon tetrachloride. At a 0.25 mol% catalyst loading the reaction is complete in 24 hours (Table 7, entry 8; 400 turnovers) and at 0.125 mol% catalyst the reaction goes to 68% conversion in 24 hours (Table 7, entry 9; 544 turnovers). The induction drops slightly to 86% ee with 0.25 mol% catalyst (Table 7, entry 8), however, the product can be obtained in 64% yield and 98% ee with a single crystallization. In this reaction, 54 mg of VAPOL was used to give 8.78 g of aziridine **3a** with 98% ee.

In the course of pursuing various applications of this catalytic AZ reaction over the last 8 years, it was found that the enantioselectivity of the AZ reaction with catalysts derived from triphenyl borate that we reported in our early work could not be reproduced.[24] For example, the induction for the reaction of the phenyl-substituted imine **1a** was originally reported as 95% ee with 10 mol% catalyst in dichloromethane[19] but now we consistently observe 89% ee with this substrate (Table 7, entry 1). Since the 95% ee for imine **1a** was reproducible at the time, considerable effort was put forth to find the source of the difference when it was first noticed in 2002. The short answer to a long story is that we never discovered the source of the difference and since the ee with rigorously purified reagents is 89% it can only be assumed that the difference is due to an impurity that was present in either the commercially purchased EDA or triphenyl borate. In an effort to further optimize the AZ reaction, an investigation was undertaken to identify the structure of the active catalyst and the optimization of the formation of the catalyst.

Table 7 Catalyst Loading Study on the AZ Reaction[a]



1a 3a

Entry	Solvent	Loading (mol%)	Yield[b] (%) of **3a**	ee (%) of **3a**
1	CH_2Cl_2	10	83	89
2	CH_2Cl_2	1	83	89
3	CH_2Cl_2	0.5	79	86
4[c]	CH_2Cl_2	0.25	–	–
5	CCl_4	10	84	93
6	CCl_4	1	86	91
7	CCl_4	0.5	88	86
8	CCl_4	0.25	88	86
9[d]	CCl_4	0.125	–	–

[a] Catalyst prepared as indicated in Scheme 5.
[b] Isolated yield.
[c] 44% conversion.
[d] 68% conversion.

It can be anticipated that a better understanding of the reaction mechanism and especially the structure of the active catalyst would benefit the optimization of this AZ reaction. A study of the relationship between the optical purity of the ligand and that of the product was carried out in order to probe the stoichiometry of the ligand and the triphenyl borate in the active catalyst. As the results in Figure 3 show, the relationship between the optical purity

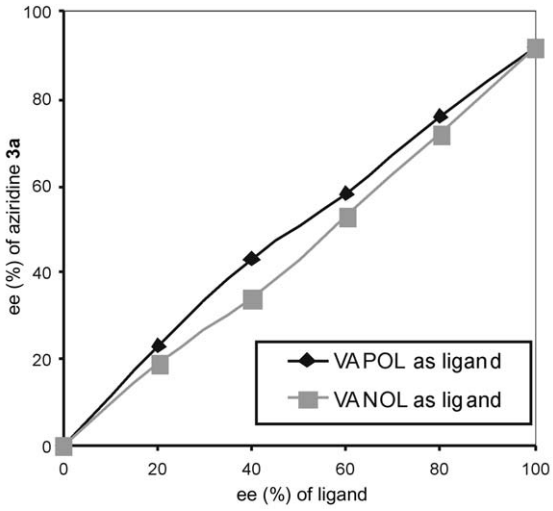


Figure 3 Study of nonlinear effects for the reaction of imine **1a** with catalyst prepared as shown in Scheme 5

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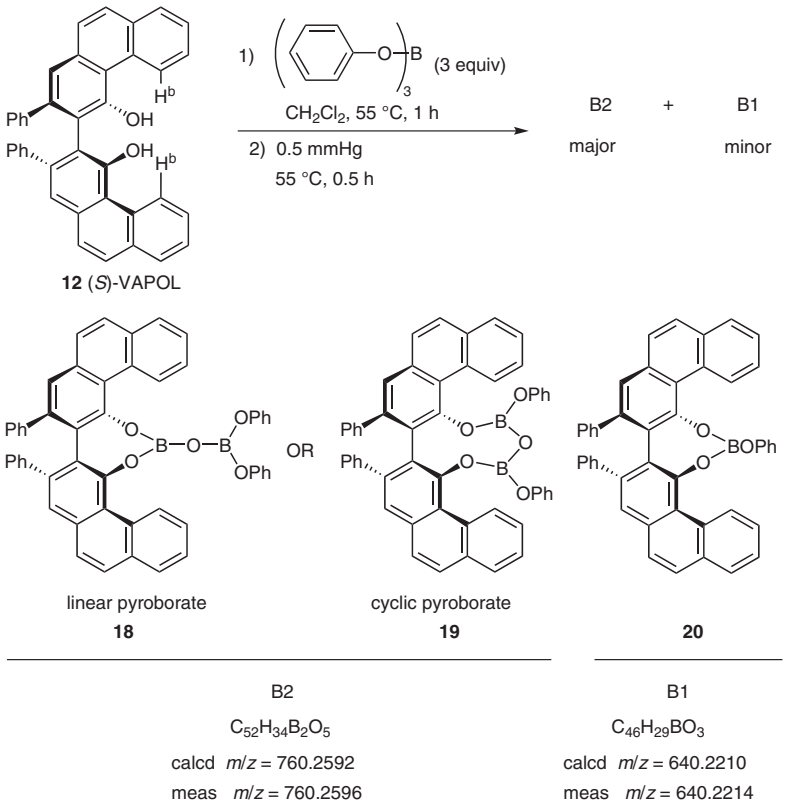
of either VANOL or VAPOL and that of aziridine **3a** is essentially linear.[24] Although the observed linearity does not disprove the association of the boron with two or more ligands, nonetheless, the results of these experiments suggest that it is likely that only one molecule of the VANOL or VAPOL ligand is involved in the active catalyst.

A series of careful spectroscopic analyses and a high-resolution mass spectrum of the catalyst prepared by the original catalyst preparation procedure shown in Scheme 5 revealed the presence of two species, as shown in Scheme 9.[24] The bay region proton in the VAPOL ligand (H^b in **12**, Scheme 9) is a convenient spectroscopic handle for probing the number of catalyst species that are generated because this proton ($\delta = 9.77$ ppm) is significantly deshielded relative to the rest of the aromatic protons of VAPOL. The catalyst prepared from VAPOL and triphenyl borate gave a mixture of two species in a ratio that ranged from 3:1 to 5:1, with the bay proton doublet for the minor species (B1) at $\delta = 9.51$ ppm and a doublet for the major species (B2) at $\delta = 9.22$ ppm. In addition, the ^{1}H NMR spectrum revealed that the major species had two phenol units per ligand and the minor had only one. High-resolution mass spectroscopy revealed ions consistent with the structures B2 and B1 shown in Scheme 9.

Since the *meso*-borate **20** was the expected structure for this catalyst, the presence of a pyroborate as the major species was quite surprising. There are two isomeric structures possible for the pyroborate and since the ^{11}B NMR spectrum revealed the presence of two different borons, the pyroborate was assigned as the linear isomer **18**. Following this discovery, the AZ reactions of imine **1a** were monitored by using several different catalysts that contain substantially enriched samples of either the B1 or B2 species prepared via different procedures (Table 8).[24] Catalysts enriched in the B1 species could be obtained by slow addition of triphenyl borate to VAPOL (Table 8, entry 2) or, better, by reaction of VAPOL with 1 equivalent of $BH_3{\cdot}SMe_2$ and 1 equivalent of phenol to give a 10:1 mixture in favor of B1 (Table 8, entry 1). The latter procedure could be used to give an 8:1 mixture of B1/B2 catalyst for VANOL (Table 8, entry 5). The VAPOL catalyst could be enhanced in B2 up to 95% purity by a procedure described below (see Table 9, entry 11).[24] The same procedure could only enhance the B2 species for VANOL to a level of 1.8:1. This could not be improved with any of the different catalyst preparation procedures that we examined. As indicated by the data in Table 8, it was found that the B2 species is indeed the active catalyst in the AZ reaction, inducing the highest selectivity and yield. For VAPOL, the % induction rises from 50% ee with a 10:1 ratio in favor of B1 (Table 8, entry 1) to 91% ee with a 20:1 ratio in favor of B2 (Table 8, entry 4). That the pyroborate B2 catalyst **18** is more active than the *meso*-borate B1 species **20** is not unexpected even though, to the best of our knowledge, pyroborates have not been examined as Lewis acids. Triphenyl borate is not a strong Lewis acid, as evidenced by the data in Table 4; however, it might be expected that the triaryl borate species B1 (**20** in Scheme 9) would be a stronger Lewis acid than triphenyl borate given the less than ideal orbital overlap in cyclic borate esters, as shown by Yasuda, Baba and



Scheme 9 B1 and B2 complexes from VAPOL and triphenyl borate

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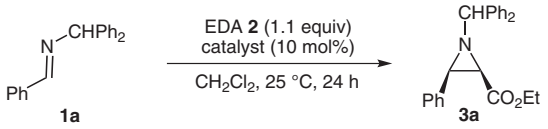
Table 8 Effect of the B2/B1 Ratio on the AZ Reaction



Entry	Ligand	Cat. Prepn[a]	Ratio B2/B1	Yield[b] (%) of **3a**	Ratio[c] *cis*/*trans*-**3a**	ee (%) of **3a**
1	(*S*)-VAPOL	A	1:10	47	–	50
2	(*S*)-VAPOL	B	1:4	66	16:1	72
3	(*S*)-VAPOL	C	4.5:1	83	>30:1	89
4	(*S*)-VAPOL	D	20:1	75	>33:1	91
5	(*S*)-VANOL	A	1:8	81	–	84
6	(*S*)-VANOL	D	1.8:1	82	100:1	93

[a] Method A: catalyst prepared by treating the ligand with $BH_3{\cdot}SMe_2$ (1 equiv) and phenol (1 equiv) in toluene at 100 °C, and then removal of all volatiles at 0.1 mmHg/100 °C; Method B: catalyst prepared by syringe pump addition of $B(OPh)_3$ (1.5 equiv) to a soln of VAPOL in toluene at 100 °C, and then removal of all volatiles at 0.1 mmHg/100 °C; Method C: catalyst prepared as indicated in Scheme 5; Method D: catalyst prepared as indicated in Table 9, entry 11.
[b] Isolated yield.
[c] Determined from the ^1H NMR spectrum of the crude reaction mixture.

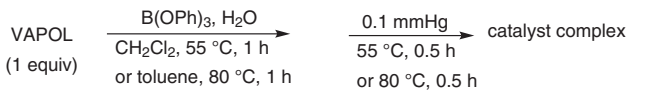
co-workers.[22] The pyroborate species **18** in Scheme 9 would be expected to be a stronger Lewis acid than the *meso*-borate **20** given the anhydride linkage in **18** where a single oxygen connects two boron atoms.

The formation of the pyroborate **18** from VAPOL and triphenyl borate was certainly unexpected especially since its formation requires an equivalent of water. The original procedure for the preparation of the aziridination catalyst (Scheme 5) involves moisture-free conditions, being performed in an oven- and flame-dried Schlenk flask and employing freshly distilled and dried solvents. Thus, it was considered most likely that the water comes from the commercially available triphenyl borate. In fact, triphenyl borate is prone to hydrolysis and most samples of commercially available triphenyl borate are partially hydrolyzed and contain free phenol. The purity of triphenyl borate obtained from a variety of suppliers was never higher than 85%. Thus, experiments probing the effect of water on the proportion of the B2 species **18** in the catalyst were carried out as shown in Table 9.[24] The results clearly indicated that the right amount of water indeed can increase the fraction of the B2 catalyst; however, the addition of too much water (1.5 equiv) leads to substantial amounts of unreacted VAPOL (Table 9, entry 6).

With the addition of a given quantity of water, the conversion of VAPOL is higher when the catalyst is prepared at 80 °C rather than at 55 °C (Table 9, entries 4 and 5 vs entries 7 and 8). After much experimentation, the optimal conditions for effecting high conversion and high selectivity for the B2 catalyst were established as including the use of 4 equivalents of triphenyl borate and 1 equivalent of water, and catalyst preparation at 80 °C (Table 9, entry 11). This procedure for catalyst preparation gave the highest induction for aziridine **3a** with 10 mol% catalyst in dichloromethane (see Table 8, entry 4).

A survey of the catalytic AZ reaction with the VAPOL and VANOL catalysts prepared by the optimized procedure with 12 imine substrates in toluene is summarized in Scheme 10.[24] All reactions were performed with 5 mol% VAPOL or VANOL catalyst. The aziridination of the same set of imines was also examined in dichloromethane.[24] A common feature of toluene and dichloromethane is the difference between imines derived from alkyl versus aryl aldehydes. In both solvents, the induc-

Table 9 Optimization of the Catalyst for Pyroborate **18**



Entry	Temp (°C)	$B(OPh)_3$ (equiv)	H_2O (equiv)	Ratio B2/B1/VAPOL
1	55	2	0	4.5:1:1.2
2	55	3	0	7.5:1:3.0
3	55	5	0	10.6:1:0.1
4	55	3	0.5	13.8:1:7.5
5	55	3	1.0	12.4:1:3.8
6	55	3	1.5	9.9:1:19.1
7	80	3	0.5	13.9:1:0.8
8	80	3	1.0	12.5:1:0.4
9	80	4	0	13.2:1:<0.1
10	80	4	0.5	13.4:1:<0.1
11	80	4	1.0	19.6:1:<0.1
12	80	5	1.0	14.6:1:<0.1

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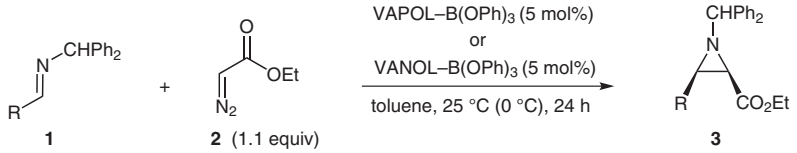
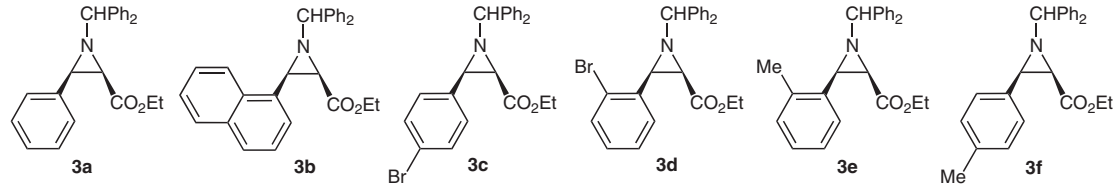
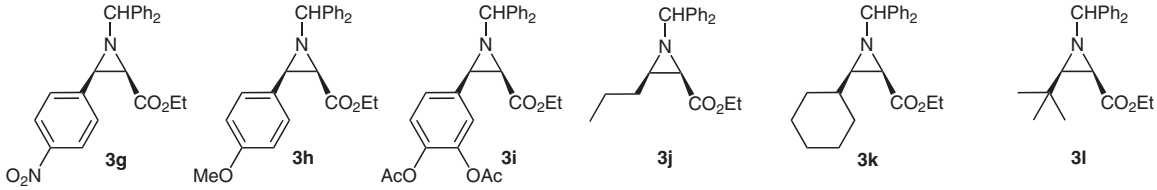




	3a		3b		3c		3d		3e		3f	
	% yield	% ee	% yield	% ee	% yield	% ee	% yield	% ee	% yield	% ee	% yield	% ee
VAPOL	82	94	76	93	78	90	37	82	63	91	80	92
VANOL	87	93	80	93	86	94	43	82	67	90	79	94



	3g		3h		3i		3j		3k		3l	
	% yield	% ee	% yield	% ee	% yield	% ee	% yield	% ee	% yield	% ee	% yield	% ee
VAPOL	79 (90)	79 (95)	51	86	87	89	40 (54)	81 (86)	73 (70)	81 (85)	72 (75)	87 (93)
VANOL	86 (93)	89 (93)	61	87	84	93	54 (60)	77 (83)	79 (81)	82 (82)	89 (58)	85 (83)

Scheme 10 AZ reaction of *N*-benzhydryl imines in toluene with catalyst prepared as indicated in Table 9, entry 11

tions are generally in the 90s for aromatic substrates and in the 80s for aliphatic substrates. The asymmetric inductions for the VAPOL–borate catalyst are higher in toluene than those in dichloromethane (7% ee higher on average), although the VANOL–borate catalyst has nearly equal asymmetric inductions in both solvents, and significantly higher yields are seen in toluene. Furthermore, the VANOL–borate catalyst gives an average of 6% higher yields than the VAPOL–borate catalyst in toluene. A decrease in the reaction temperature from room temperature to 0 °C has a big impact on the *p*-nitrophenyl-substituted imine **1g** (79% ee to 95% ee) when the reaction is catalyzed by the VAPOL–borate catalyst, while only a small increase in ee was observed with the VANOL–borate catalyst. In contrast, the same lowered temperature only gave a small improvement in the asymmetric inductions for alkyl imines (up to 6% increased ee).[24] One of the more interesting aspects of the data in Scheme 10 is the closeness of the asymmetric inductions for the VAPOL and VANOL ligands. Over the 12 substrates in Scheme 10, the average difference is 0.75% ee. Given the difference in the size of the chiral pocket of the two ligands (Figure 1), the fact that both ligands give nearly the same selectivity profile over the entire set of substrates is truly remarkable.

The benzhydryl group on the nitrogen renders all 12 of the substrates in Scheme 10 as solids that can be crystallized from hexanes or from hexanes and ethyl acetate. This propensity towards crystallinity can be taken advantage of in enhancing the optical purity of the aziridines. As indicated in Table 10, the optical purity of 10 of the aziridines can be improved to greater than 99% ee with a single crystallization. The *o*-bromophenyl-substituted aziridine **3d** can be improved to 98.6% ee and the *n*-propyl-substituted aziridine **3j** can be improved to 96.6% ee in a single crystallization. In each case, no *trans*-aziridine was observed after crystallization.

Table 10 Enhancement of the Optical Purity of *N*-Benzhydrylaziridines by Crystallization

	3a	3b	3c	3d	3e	3f
Starting % ee	94	89	94	85	91	87
1st Crop (% recovery)	62	55	76	65	74	81
% ee of 1st Crop	99.4	99.9	99.4	98.6	99.3	99.9
	3g	**3h**	**3i**	**3j**	**3k**	**3l**
Starting % ee	94.5	87	92.5	86	83	87
1st Crop (% recovery)	74	81	67	40	80	76
% ee of 1st Crop	99.7	99.9	99.0	96.6	99.1	99.7

2.3 Deprotection and Activation of Aziridine-2-carboxylates

The ring-opening reactions of aziridines can be divided into two classes: those that involve activated aziridines and those that involve nonactivated aziridines.[1] The former types of aziridines have electron-withdrawing groups (such as carbonyl or sulfonyl) on the nitrogen rendering the nitrogen a good leaving group and this, coupled

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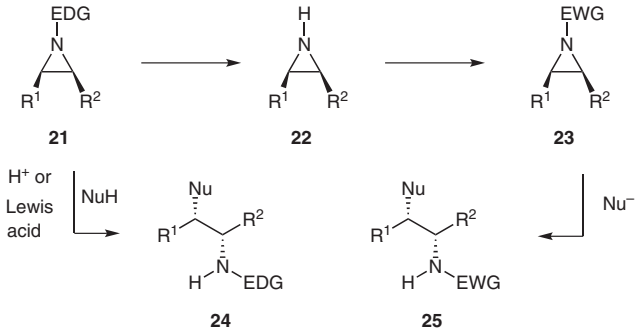
with the ring strain, allows for the direct opening of aziridines of the type **23** with nucleophiles (Scheme 11). The ring opening of aziridines of the type **21** with electron-donating groups (such as alkyl, benzyl or benzhydryl), on the other hand, requires the activation of the nitrogen with either a Brønsted or Lewis acid. Both processes generally proceed with inversion.



Scheme 11 Ring opening of aziridines

The studies that lead to the original discovery of the AZ reaction and which ultimately enabled its optimization revealed that the two phenyl groups of the benzhydryl group were essential to obtaining both high yields and high asymmetric inductions (see Table 1). While *N*-benzhydrylaziridines should serve as useful substrates in the ring-opening reaction mediated by Lewis acids or with Brønsted acids, they are not activated aziridines and thus would not be expected to undergo direct ring opening with nucleophiles.

Thus, in an effort to access activated aziridines directly from the AZ reaction, we attempted to look for surrogates for the benzhydryl group that would be electronically modified isosteres and, on this basis, the imines **26** and **27** were identified as targets (Figure 4). Unfortunately, imines **26** and **27** were completely unreactive in the AZ reaction with the catalyst generated as indicated in Scheme 5.[25] The failure of **27** was particularly disappointing, since the diphenylphosphoryl group is a known and effective activating group for the ring opening of aziridines.[5b,26]

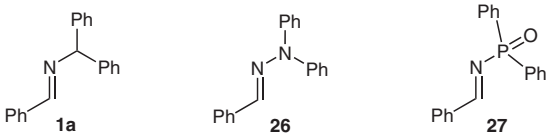
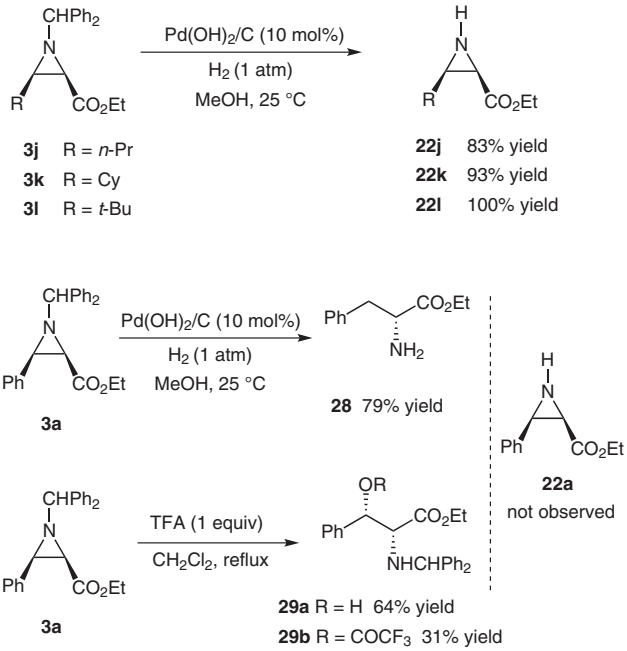


Figure 4 Surrogates for *N*-benzhydryl imine **1a**

Given the fact that imines with an electron-withdrawing group as the N-substituent would not participate in the AZ reaction, access to activated aziridines was then pursued via a two-step protocol involving deprotection of the *N*-benzhydrylaziridines and then introduction of an electron-withdrawing group, as outlined in Scheme 11. Since the benzhydryl group is doubly benzylic, it was not a surprise to find that *N*-benzhydrylaziridine-2-carboxylates undergo hydrogenolysis of the benzhydryl group to give the corresponding *N*-H aziridines **22** (Scheme 12). The optimal process involves Pearlman's catalyst and gives *cis*-3-alkylaziridine-2-carboxylates of the type **22j**, **22k** and **22l** in excellent yields;[27] however, the situation is quite different with the phenyl-substituted aziridine **3a**. Here, the exclusive product results from both the ring opening of the aziridine and the cleavage of the *N*-benzhydryl group to give D-phenylalanine ethyl ester (**28**) in 79% yield. In the case of **3a**, the competition is between hydrogenolysis of a doubly benzylic group versus a singly benzylic group that also contains the ring strain of the aziridine. In this case, both processes are facile and the *N*-H aziridine **22a** was not observed. Another approach to effect the cleavage of a benzhydryl group from nitrogen is to employ a strong Brønsted acid, which is driven by the stability of the diphenylmethyl cation; however, with aziridine **3a** the reaction with trifluoroacetic acid is dominated by the ring strain since it gives exclusive opening of the aziridine ring and the benzhydryl group remains intact to give the β-oxygenated α-amino esters **29** in high yield (95%).[28]



Scheme 12 Deprotection of *N*-benzhydrylaziridines

Given the failure of hydrogenolysis and Brønsted acids to cleave the benzhydryl group from 3-arylaziridine-2-carboxylates without ring opening (Scheme 12), we developed a new method to remove the benzhydryl group from aziridines.[27] This work was prompted by an observation made by Ito and co-workers on the oxidation of C–H bonds alpha to nitrogen with ozone and the finding that the C–H bonds in 3-phenylaziridines are particularly resistant to oxidation.[29] With this information as a lead, we found that a variety of *N*-benzhydrylaziridine-2-carboxylates could be deprotected to give the *N*-H aziridines, including both those that had alkyl and aryl groups in the

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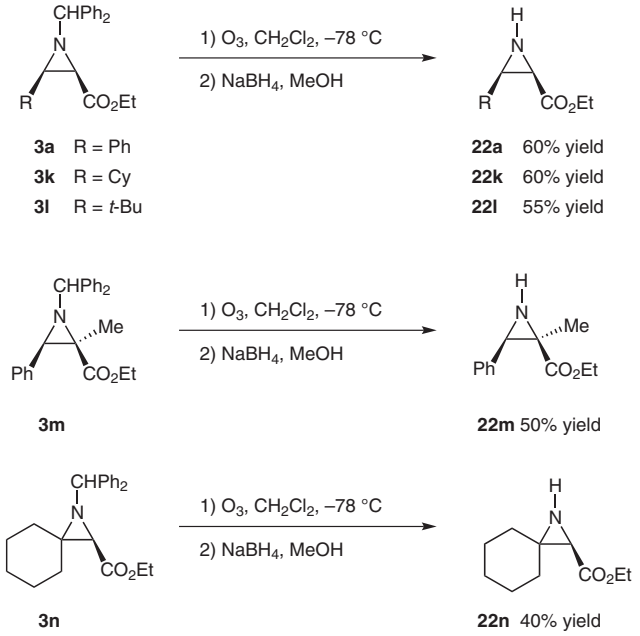
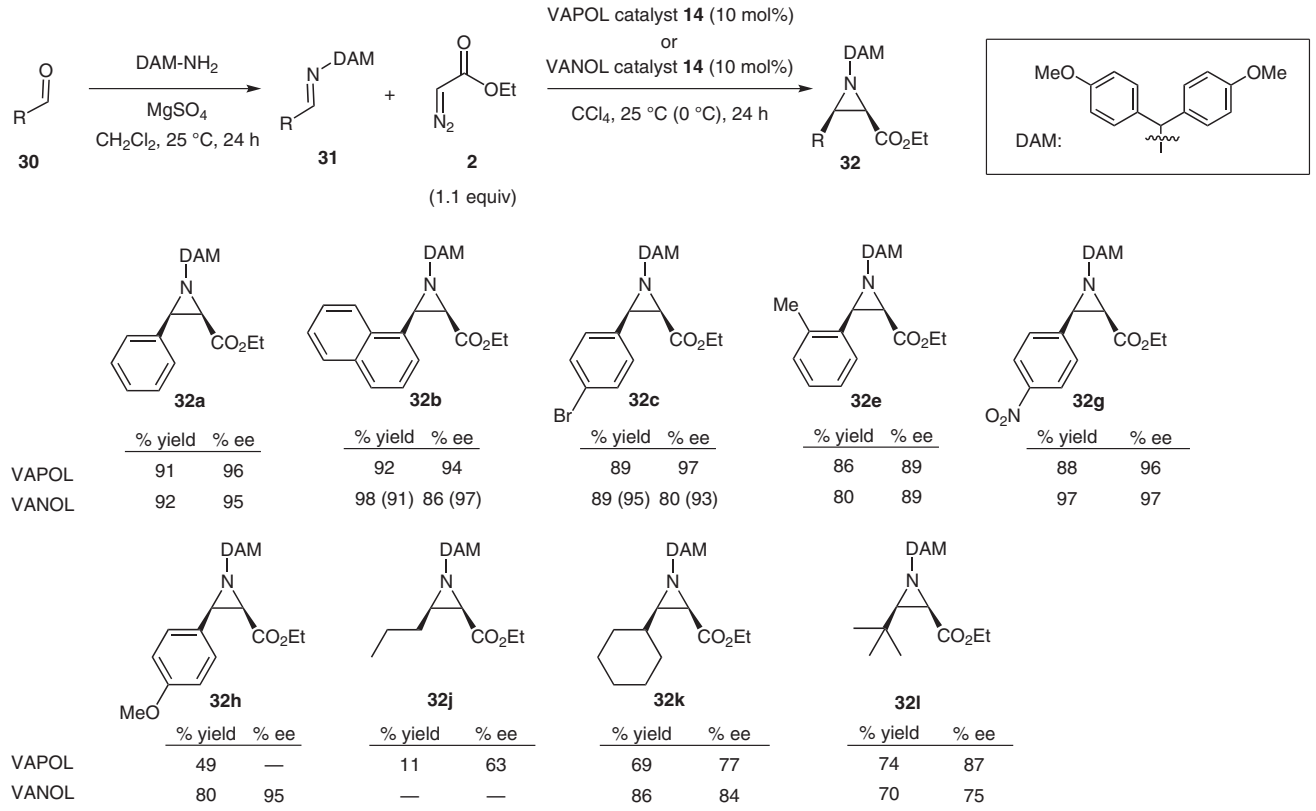


Scheme 13 Ozonolysis of *N*-benzhydrylaziridines

3-position (Scheme 13). Despite substantial efforts to optimize this process, the yields for the ozone-mediated deprotection were only moderate to good (40–60%).

Although ozonolysis was effective in deprotecting a variety of substituted *N*-benzhydrylaziridines (Scheme 13), the yields were not high and thus efforts to establish an effective entry to *N*-H aziridines continued. The best solution realized to date involves the use of the dianisylmethyl (DAM) protecting group for the aziridine nitrogen. Although this group has previously been used as a protecting group for nitrogen,[30] it had not been used for protecting aziridine nitrogens and thus nothing was known about its ability to be removed from an aziridine without ring opening. It was known that the DAM group could be cleaved from amines with a Brønsted acid under conditions that were milder than those required for the benzhydryl group and this is presumably related to the greater stabilization of the resulting dianisylmethyl cation. Thus, it was hoped that the chemoselectivity in the reaction of *N*-benzhydrylaziridine **3a** with a Brønsted acid (see Scheme 12) could be reversed with a DAM protecting group, i.e. that the protecting group on nitrogen be removed and the aziridine ring not be opened.

This all, of course, depends on whether the catalytic AZ reaction with *N*-DAM imines is as effective as that with *N*-benzhydryl imines and, as illustrated by the data in Scheme 14, this is generally the case.[28] The *N*-DAM imines are prepared from the appropriate aldehyde **30** by reaction with the commercially available dianisylmethylamine in the presence of a drying agent. As was the case for the *N*-benzhydryl imines **1** (Scheme 5), all of the *N*-DAM imines **31** were purified by crystallization, except the one prepared from *n*-butanal which was an oil and the inability to purify this imine may account for the poor results (see **32j**, Scheme 14). The VANOL and VAPOL catalysts for the reactions of the *N*-DAM imines shown in Scheme 14 were prepared as indicated in Scheme 5. As



Scheme 14 Catalytic AZ reaction with *N*-DAM imines

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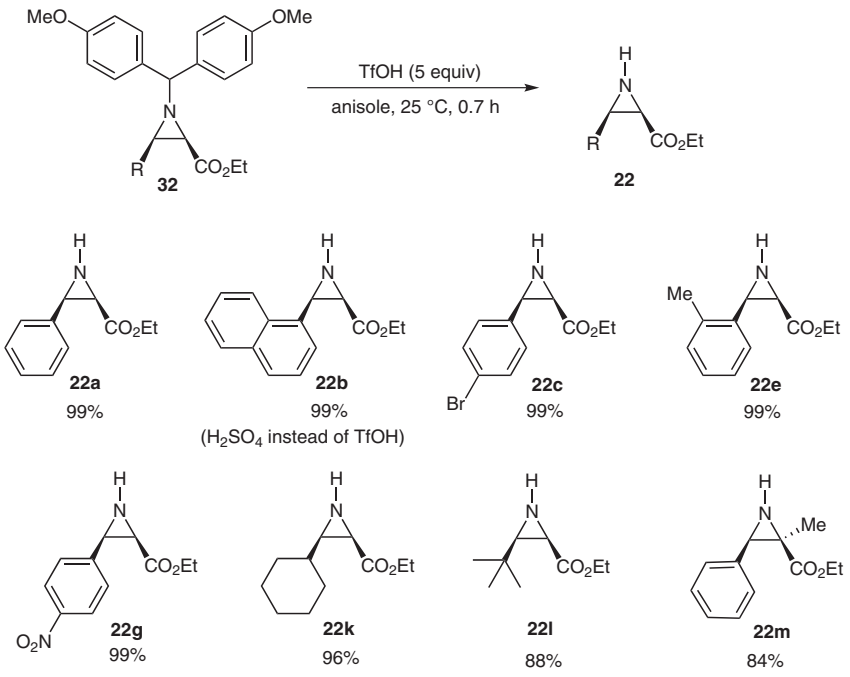


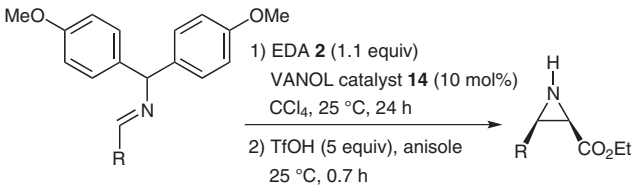
Scheme 15 Deprotection of *N*-DAM aziridines with triflic acid

can be seen from the data, the asymmetric inductions and yields are comparable or slightly higher with the *N*-DAM imines than the *N*-benzhydryl imines, with the exception of the imine derived from *n*-butanal. The AZ reactions with the VANOL and VAPOL catalysts generally give similar asymmetric inductions and the VANOL catalyst would typically give higher yields. It is important to note that with the exception of the aziridine obtained from *n*-butanal, the optical purity of all of the aziridines shown in Scheme 14 can be enhanced to greater than 99% ee with a single crystallization from dichloromethane and hexanes.[28]

As indicated by the data in Scheme 15, the addition of two methoxy groups on the benzhydryl substituent does in fact reverse the relative propensities of ring opening versus deprotection upon reaction of *N*-benzhydrylaziridines with Brønsted acids (Scheme 12 vs Scheme 15). In fact, three different acid conditions were developed[28] and the results from deprotection of *N*-DAM aziridines **32** with triflic acid in anisole are shown in Scheme 15. Excellent yields of *N*-H aziridines **22** were obtained with both alkyl- and aryl-substituted aziridines. The only exception is the *p*-methoxyphenyl-substituted aziridine **32h** (Scheme 14), which could not be deprotected without also causing ring opening. These optimized acidic conditions were not found to be useful for deprotection of simple *N*-benzhydrylaziridines as complex mixtures of products were observed.

The generation of *N*-H aziridines from the AZ reaction of *N*-DAM imines and EDA can be greatly simplified by cleavage of the DAM group without purification of the intermediate *N*-DAM aziridines (Scheme 16). The same asymmetric inductions and the same or slightly better overall isolated yields of *N*-H aziridines **22** were obtained as compared to the two-step procedure (Schemes 14 and 15). Thus, purification of the *N*-DAM aziridines **32** is unnecessary.

The activation of aziridines is usually achieved by installation of carbonyl or sulfonyl groups on the nitrogen.[1] Selected examples of activation of the *N*-H aziridines **22** with Boc, tosyl and Fmoc groups are shown in Scheme 17.[28] A number of published procedures were evaluated for the installation of each activating group to determine the optimal procedure in each case for these aziridines, and these procedures are indicated in Scheme 17. Excellent yields were observed for each activating group. It was found that purification of the *N*-H aziridines prior to activation was unnecessary. For example, the overall yield of the *N*-Boc aziridine **33b** from the *N*-DAM aziridine **32b** is the same whether or not the intermediate *N*-H aziridine **22b** is purified. There was no erosion of the % ee and no evidence for isomerization to *trans*-isomers under the acidic deprotection conditions and the basic reprotection protocols.



31a R = Ph
31k R = Cy

22a 92% overall yield; 94% ee
22k 89% overall yield; 83% ee

Scheme 16 One-step synthesis of *N*-H aziridines

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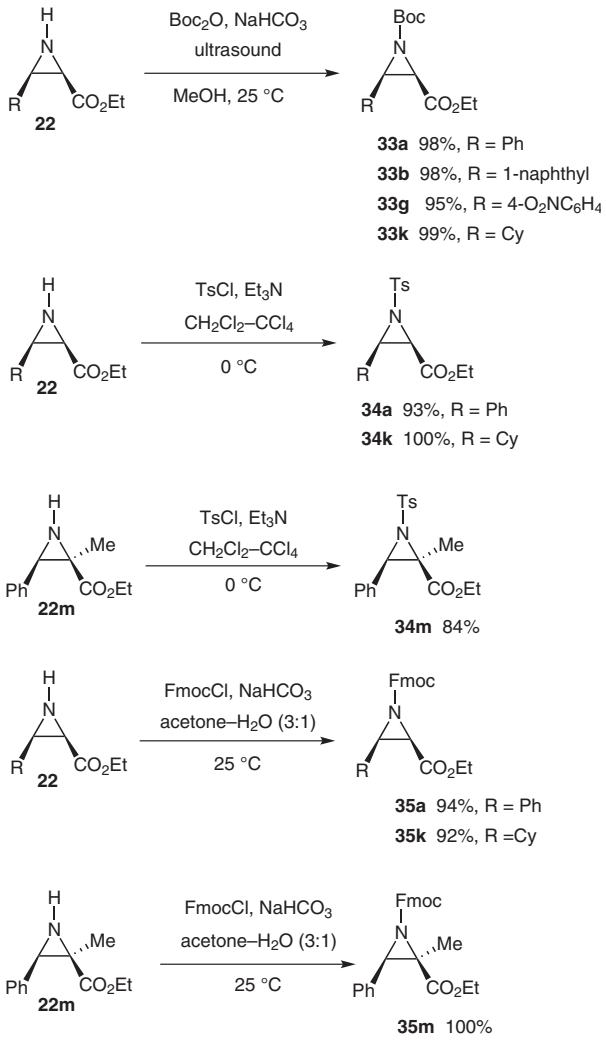
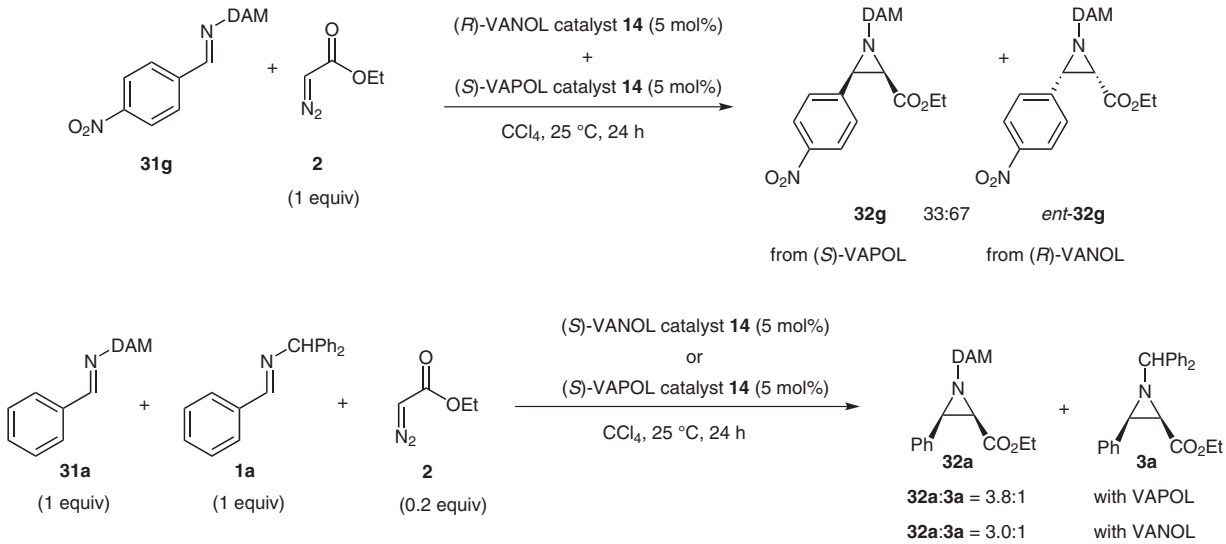


Scheme 17 Synthesis of activated aziridines from *N*-H aziridines

During the study of the aziridination of *N*-DAM imines, an opportunity was taken to quantify the difference in reaction rates between the VANOL and VAPOL ligands.[28] The aziridination of the *p*-nitrophenyl-substituted imine **31g** was carried out with a mixture of 5 mol% of the catalyst prepared by the procedure shown in Scheme 5 with (*R*)-VANOL and 5 mol% of the same catalyst prepared from (*S*)-VAPOL (Scheme 18). This competition produced a 1:2 mixture of the two enantiomers with the VANOL-induced enantiomer as the major, thus revealing that the reaction with the catalyst from VANOL is twice as fast as that with the VAPOL catalyst. This experiment was designed with the knowledge that neither the VANOL nor the VAPOL catalyst formed with triphenyl borate exhibits any nonlinear effects and thus each catalyst is deemed likely to contain only one molecule of the ligand (Figure 3).[24] Information was also sought on the relative reactivity of the *N*-DAM imines **31** versus the *N*-benzhydryl imines **1** (Scheme 18).[28] To this end, a competition was set up that involved the reaction of 1 equivalent each of the *N*-DAM imine **31a** and the *N*-benzhydryl imine **1a** with 0.2 equivalents of EDA. Surprisingly, reaction of the *N*-DAM imine **31a** was 3.8 times faster with the VAPOL catalyst and 3.0 times faster with the VANOL catalyst than reaction of the *N*-benzhydryl imine **1a**. The reason for the increased reaction rate of the VANOL catalyst over that of the VAPOL catalyst and for the increased reaction rate of the *N*-dianisylmethyl imine over the *N*-benzhydryl imine is not clear at this time.

The observation that the reaction with the catalyst prepared from VANOL is faster than that with the catalyst prepared from VAPOL (Scheme 18) suggests that it might be possible to employ lower catalyst loadings with VANOL. This proved to be the case, although only to a small degree as indicated by the catalyst loading study summarized in Table 11.[28]

The catalyst loading can be reduced for both ligands to 1 mol% without any loss in yield or induction. Further lowering of the loading to 0.25 mol% resulted in the reaction going to completion for the VANOL catalyst but only to 80% completion for the VAPOL catalyst. This was the



Scheme 18 Competition experiments with *N*-DAM imines

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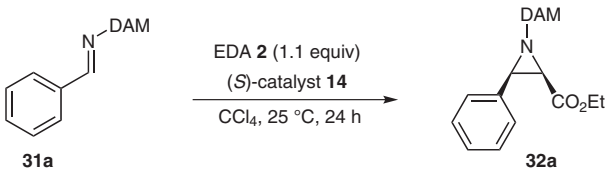
Table 11 Catalyst Loading Study with *N*-DAM Imine **31a**



31a **32a**

Entry	Ligand	Loading (mol%)	Conversion (%)	Yield (%) of **32a**	ee (%) of **32a**
1	VANOL	10	100	92	95
2	VANOL	1	100	92	96
3	VANOL	0.5	100	92	92
4	VANOL	0.25	100	89	90
5	VANOL	0.1	10	–	–
6	VAPOL	10	100	91	96
7	VAPOL	2	100	95	96
8	VAPOL	1	100	89	96
9	VAPOL	0.5	100	82	95
10	VAPOL	0.25	80	72	87

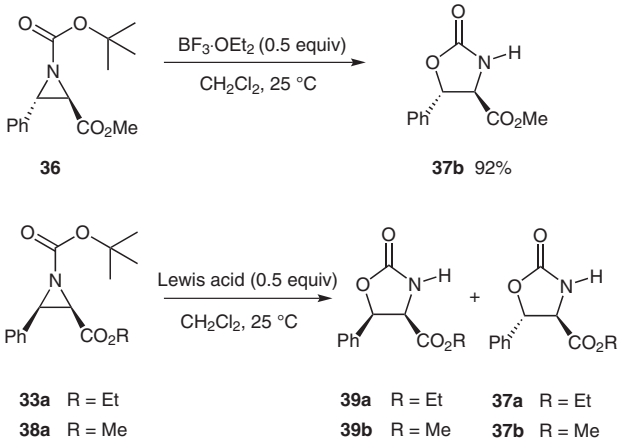
loading limit since the reaction with 0.1 mol% VANOL catalyst only went to 10% completion. The reaction with 0.25 mol% of the VANOL catalyst was carried out on 11.6 g of imine **31a** and employed only 39 mg of VANOL, and in 400 turnovers gave the aziridine **32a** in 89% yield and 90% ee. The optical purity of this material could be enhanced to 97–98% ee with two crystallizations from dichloromethane and hexanes. Finally, it should be mentioned that the ligand can be recovered in high yields. For example, VAPOL was recovered in 95% yield and in >99% ee from the reaction indicated in entry 7 of Table 11.

3 Applications of Catalytic Asymmetric Aziridination

3.1 Ring Expansion of Aziridines to Oxazolidinones

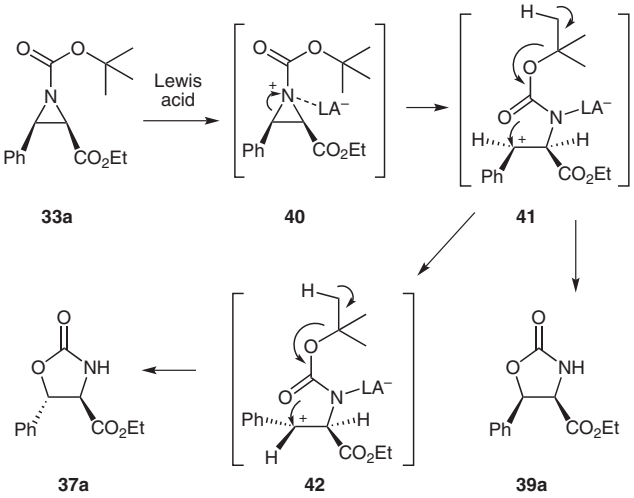
The Lewis acid mediated ring expansion of aziridines to oxazolidinones is known for aziridines that have carbonyl substituents on the nitrogen.[31] In many of the known cases the ring expansion occurs with retention of configuration and, as a consequence, this process becomes synthetically useful since it provides access to β-hydroxy amino functions that are diastereomerically complementary to those obtained by ring opening of aziridines with oxygen nucleophiles, since the latter occurs with inversion of configuration (Scheme 19 vs Scheme 11). For example, the ring expansion of the *N*-Boc-protected *trans*-3-phenylaziridine-2-carboxylate **36** has been reported to give exclusively the *trans*-oxazolidinone **37b** in 92% yield (Scheme 19).[31a] Curiously, there were no known examples of a similar ring expansion of *cis*-aziridine-2-carboxylates with an aryl group in the 3-position which caught our attention since these compounds were now readily available substrates as a result of the success of the AZ reaction. Based on the literature, we were surprised to find that the ring expansion of the aziridines **33a** and **38a** is not stereoselective since mixtures of *cis*- and *trans*-oxazolidinones **39** and **37** were obtained with either $BF_3{\cdot}OEt_2$ or $Cu(OTf)_2$ as the Lewis acid (Scheme 19).[28]

Despite the fact that retention is normally observed for the ring expansion of aziridines to oxazolidinones, both concerted S_Ni and two-step S_N1 mechanisms have been proposed for this process;[31] however, the ring expansion of aziridine **33a** clearly occurs via an S_N1 mechanism, as shown in Scheme 20. Another mechanism by which the *trans*-oxazolidinone **37a** could have been formed from the ring expansion of the *cis*-aziridine **33a** is via a concerted



R	Lewis acid	% yield **39** + **37**	ratio **39**:**37**
Et	$BF_3{\cdot}OEt_2$	84	3.2:1
Et	$Cu(OTf)_2$	99	0.7:1
Me	$BF_3{\cdot}OEt_2$	75	2.1:1
Me	$Cu(OTf)_2$	85	0.5:1

Scheme 19 Ring expansion of *N*-Boc aziridines



Scheme 20 Mechanism for oxazolidinone formation

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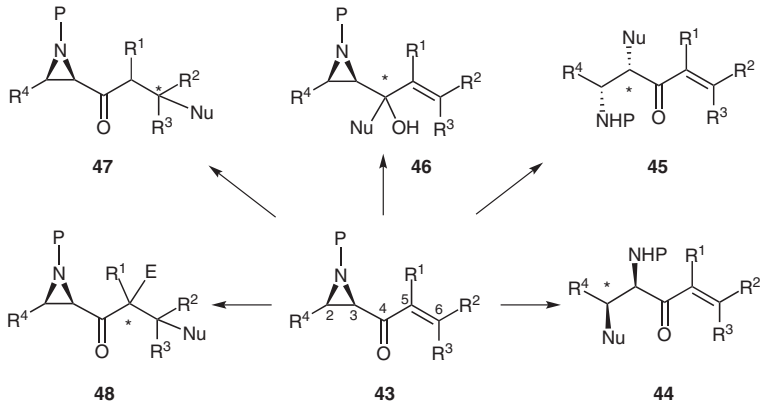
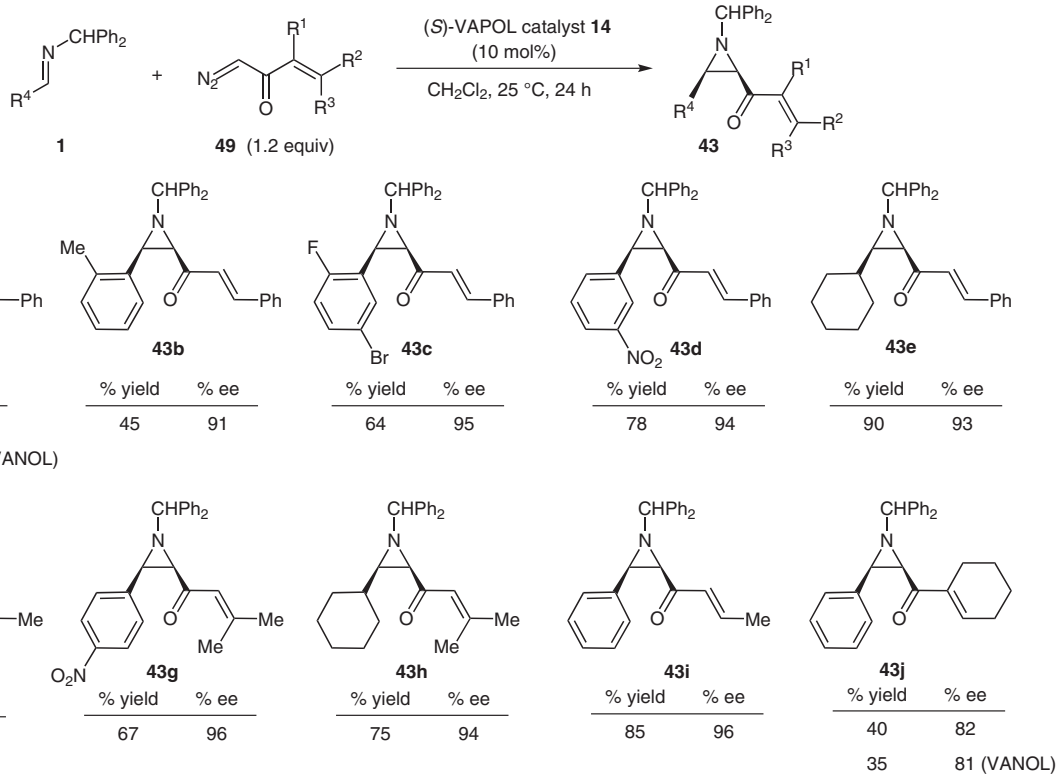
ring expansion with retention to the *cis*-oxazolidinone **39a** and then subsequent epimerization; however, this was shown not to be the case since this would produce the enantiomer of **37a**.[28]

3.2 Asymmetric Aziridination with Diazomethyl Vinyl Ketones

Aziridinyl vinyl ketones of the type **43** are attractive synthetic intermediates which have the potential to provide a platform that can serve as an entry point for a diverse array of five-carbon fragments. It is envisioned that it may be possible to utilize the chirality at the aziridine to stereoselectively introduce chiral centers at each of the five carbons in the synthon. For example, nucleophilic opening of the aziridine at the C-2 and C-3 positions could be used to control the stereochemistry of the newly functionalized carbon in **44** and **45**, respectively (Scheme 21). Nucleophilic addition to the ketone would generate a new chiral center at C-4 which ideally could occur under the right conditions to selectively give either epimer. Propagation of the stereochemical information of the aziridine during a Michael addition would lead to a new chiral center at C-6 in **47**. Finally, alkylation of the ketone or as a second step in the Michael addition would generate the chiral center at C-5 in **48**. All of the chemistry outlined in Scheme 21 existed only on paper when we began our work and in fact only one example of an acyclic aziridinyl vinyl ketone was known at the time and its chemistry had not been explored.[32]



Scheme 21 Chirality transfer in aziridinyl vinyl ketones



Scheme 22 Catalytic AZ reaction with diazomethyl vinyl ketones

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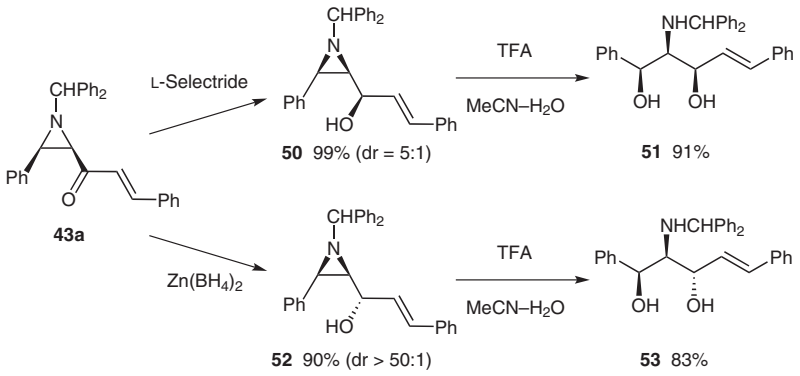


Scheme 23 Chelation-controlled and nonchelation-controlled reduction of **43a**

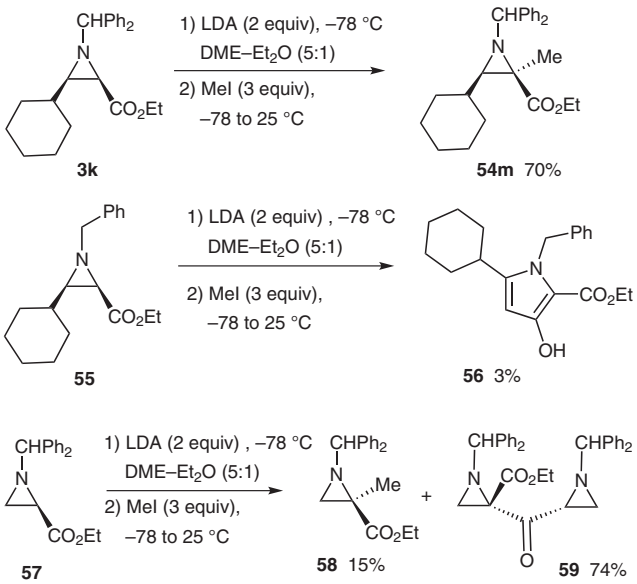
The catalyst that was developed for the AZ reaction of imines with EDA (Scheme 5) proved to be equally effective for the aziridination with diazomethyl vinyl ketones of the general type **49**. We examined a variety of diazomethyl vinyl ketones and some of the results are shown in Scheme 22.[33] As can be seen, the reaction generally gives the aziridinyl vinyl ketones **43** in good to excellent yields with excellent asymmetric inductions, and with good to excellent diastereoselectivity (not shown). The only exception is for the reaction of the diazo compound containing a cyclohexenyl group where much lower yields of **43j** were observed, which is a function of the fact that a number of other products were formed.

As an initial foray into a study aimed at the development of aziridinyl vinyl ketones as synthons for the asymmetric synthesis of five-carbon amine fragments, the diastereoselective reduction of the ketone unit in **43a** was examined, as shown in Scheme 23.[33] The chelation-controlled reduction[34] with zinc borohydride gave compound **52** with greater than 50:1 selectivity despite the existence of the large benzhydryl protecting group on the nitrogen, while the nonchelation-controlled reduction could be effected with L-Selectride® in quantitative yield with a 5:1 selectivity for the diastereomer **50**, which would be readily separable from **52**. The hydrolytic opening of the aziridine rings in **50** and **52** occurred with complete inversion and gave the *syn*,*syn*-amino diol **51** and the *syn*,*anti*-amino diol **53**, respectively.

3.3 Diastereoselective Alkylation of *cis*-Aziridine-2-carboxylates

The alkylation of aziridine-2-carboxylates alpha to the ester is an extremely limited reaction since the enolates of these compounds are prone to undergo Claisen condensations and ring-opening reactions.[35] The *cis*-3-substituted aziridine-2-carboxylates that are the products of the AZ reaction are an exception to this limitation.[36] For example, the *N*-benzhydrylaziridine 3k can be deprotonated with lithium diisopropylamide and the resulting enolate alkylated with iodomethane to give the tetrasubstituted aziridine 54m in 70% yield (Scheme 24). The presence of the *N*-benzhydryl group and the *cis* substituent in the 3-position are both important for the success of the alkylation. This is illustrated in the attempted alkylation of the *N*-benzylaziridine 55 under the same conditions as that for the alkylation of 3k. No aziridine products or recovered aziridine 55 was present in the crude reaction mixture and the only product, among the many that are formed, that could be isolated and identified was the pyrrole 56.[36] Likewise, the alkylation of the *N*-benzhydrylaziridine 57, lacking a substituent in the 3-position, is not successful since under the same conditions it gives the Claisen condensation product 59 as the major product of the reaction.

The alkylation of the *cis*-3-substituted *N*-benzhydrylaziridines occurs with retention of configuration, as confirmed by X-ray crystallography.[36] This argues against the planar structure **62** for the enolate and suggests that the enolate is pyramidalized, as indicated by the structure **60** (Scheme 25). No evidence could be found for epimerization of the pyramidal enolate to the diastereomer **61**. If the enolate of **3a** (R = Ph) is generated at –78 °C and then warmed to 0 °C for 2 hours before quenching with water, the aziridine **3a** is recovered in 98% yield with complete retention of stereochemistry.



Scheme 24 Alkylation of aziridine-2-carboxylates

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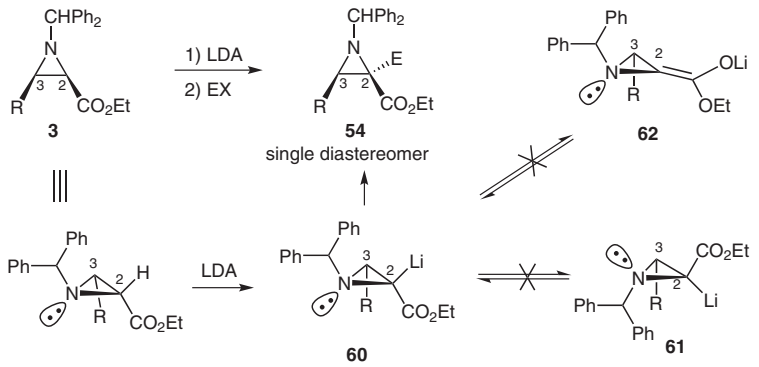


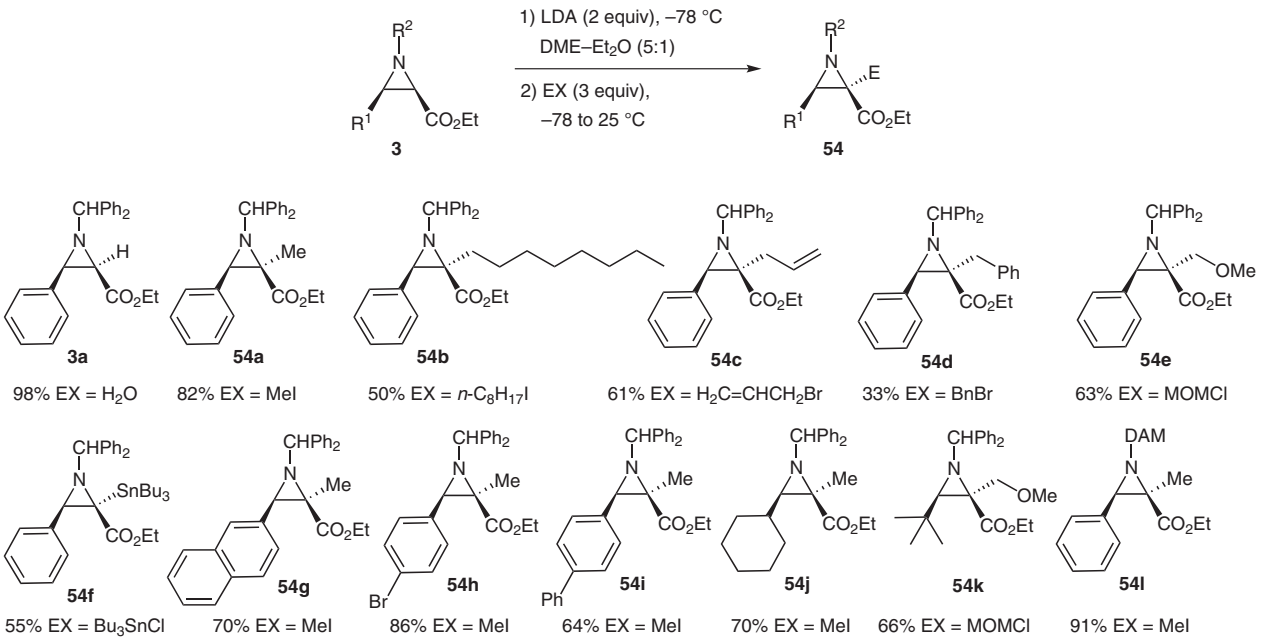
Scheme 25 Enolate geometry of the anion of **3**

The scope of the alkylation reaction with a variety of electrophiles and aziridines was examined and some of the results are shown in Scheme 26.[36] With one exception, all of the alkylations indicated in Scheme 26 gave a single diastereomer which was assigned the *cis* stereochemistry indicated in **54** on the basis of the X-ray structure of the derivative in which R^1 = phenyl and R^2 = benzhydryl.

The exception is the reaction in which tributyltin chloride was the electrophile. In this case, an 18% yield of an isomeric product was isolated which has been tentatively assigned as that resulting from O-alkylation. Note that both aryl- and alkyl-substituted aziridines can be successfully alkylated, as well as both benzhydryl- and dianisylmethyl-protected aziridines.[28,36]

3.4 Synthetic Applications of the Catalytic Asymmetric Aziridination Reaction

One of the most important applications of aziridine-2-carboxylates is their reductive ring opening to give α-amino acids. The synthesis of L-3,4-dihydroxyphenylalanine (L-DOPA) outlined in Scheme 27 takes advantage of this process and nicely illustrates the utility of the catalytic AZ reaction of imines with diazo compounds.[19] This synthesis of L-DOPA (**65**), a compound which is used in the management of Parkinson's disease and as a component in marine adhesives, is accomplished in only four steps from the diacetate **63** of protocatechualdehyde (Scheme 27). Condensation of aldehyde **63** with benzhydrylamine gave the imine **1i**, which was obtained in 66% yield after purification by crystallization. The catalytic AZ reaction of **1i** with EDA (**2**) was accomplished with 2.5 mol% of the catalyst prepared from (*R*)-VAPOL according to the procedure shown in Scheme 5 and gave the aziridine **3i** in 85% yield and 96% ee, with a 50:1 *cis*/*trans* selectivity. The optical purity of the aziridine could be easily enhanced to >99% ee by crystallization from hexanes and dichloromethane. Collection of the first crop gave an 85% recovery of material that had >99% ee. Reductive ring opening with palladium black and formic acid occurred



Scheme 26 Alkylation of *N*-benzhydryl- and *N*-dianisylmethylaziridines

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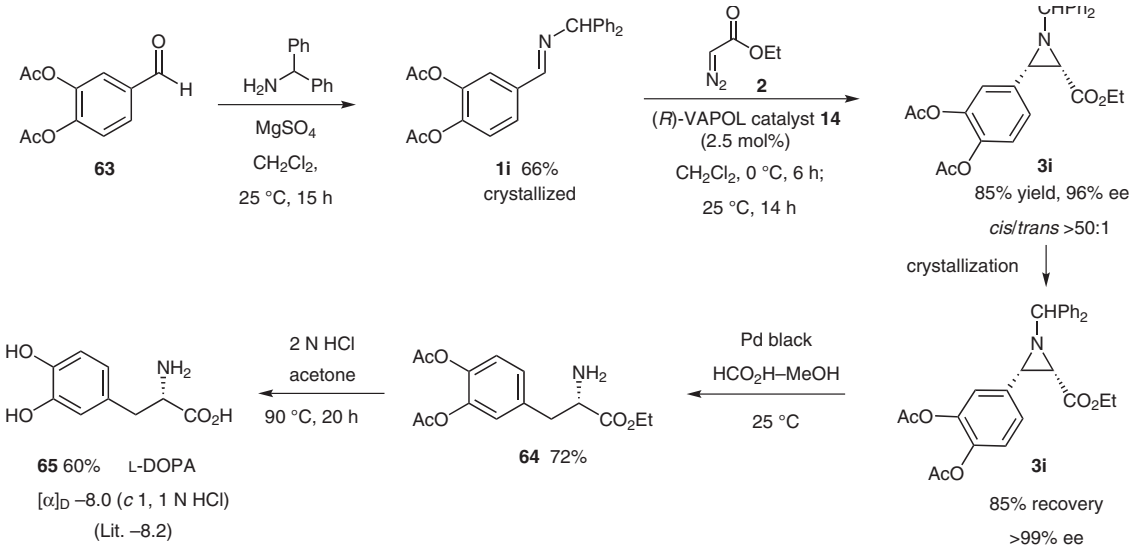
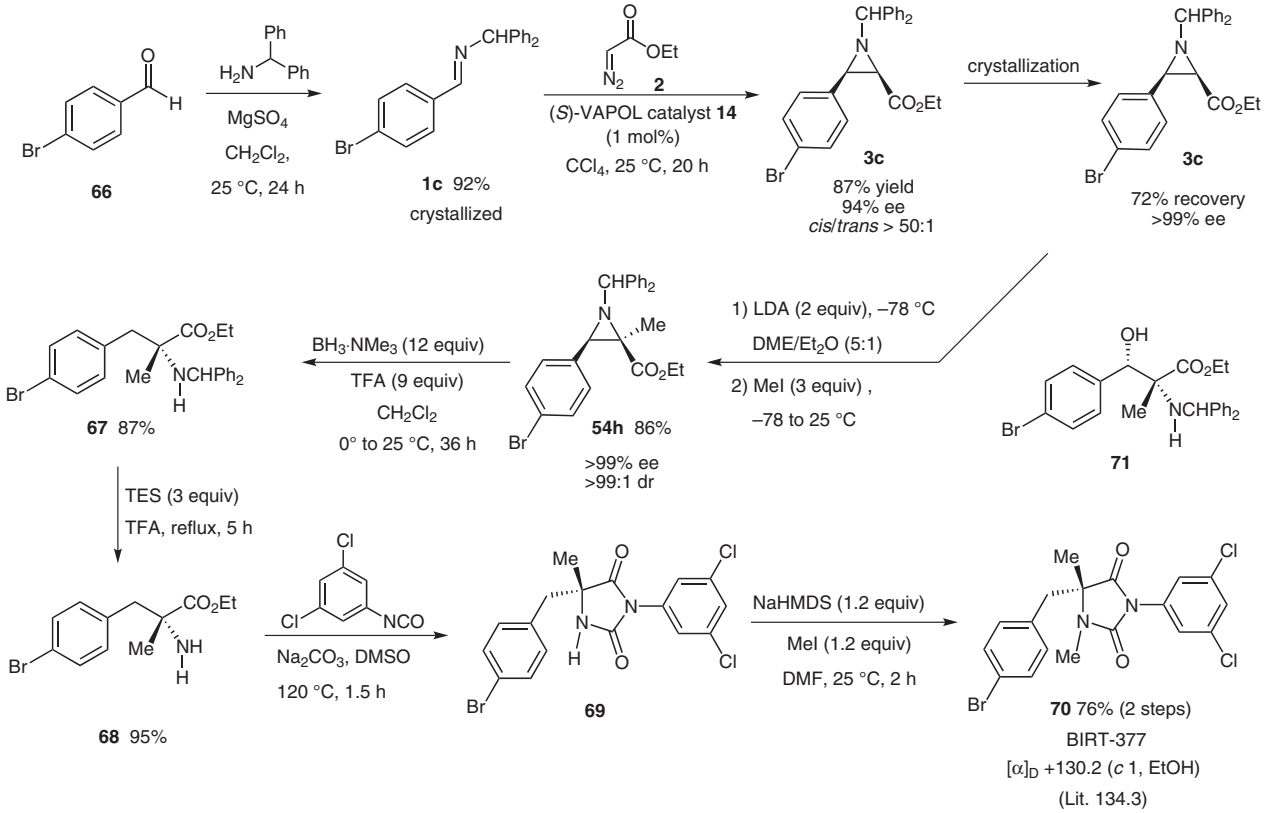


Scheme 27 Synthesis of L-3,4-dihydroxyphenylalanine (L-DOPA, **65**)

concomitant with hydrogenolysis of the benzhydryl group to give the α-amino ester **64**, and then hydrolysis of all the ester functions gave L-DOPA (**65**) in optically pure form.

α-Amino acids that are tetrasubstituted at the α-carbon are popular tools used to control conformation in peptides and hence their biological and pharmaceutical properties.[37] The synthesis of BIRT-377 (**70**) shown in Scheme 28 serves to highlight the synthetic importance of the α-alkylation process that was developed for *cis*-substituted aziridine-2-carboxylates that are the products of the AZ reaction (see Scheme 26).[36,38] In this particular case, this alkylation is highlighted in the synthesis of a tetrasubstituted α-amino acid that is used in the synthesis of the LFA-1 antagonist BIRT-377 which has been developed as an agent for the treatment of inflammatory and immune disorders. The catalytic AZ reaction of the *N*-benzhydryl imine of *p*-bromobenzaldehyde was performed with 1 mol% of catalyst **14** prepared from (*S*)-VAPOL and gave aziridine **3c** in 87% yield and 94% ee. The optically purity of this aziridine could be enhanced to >99% ee by a single



Scheme 28 Synthesis of BIRT-377 (**70**)

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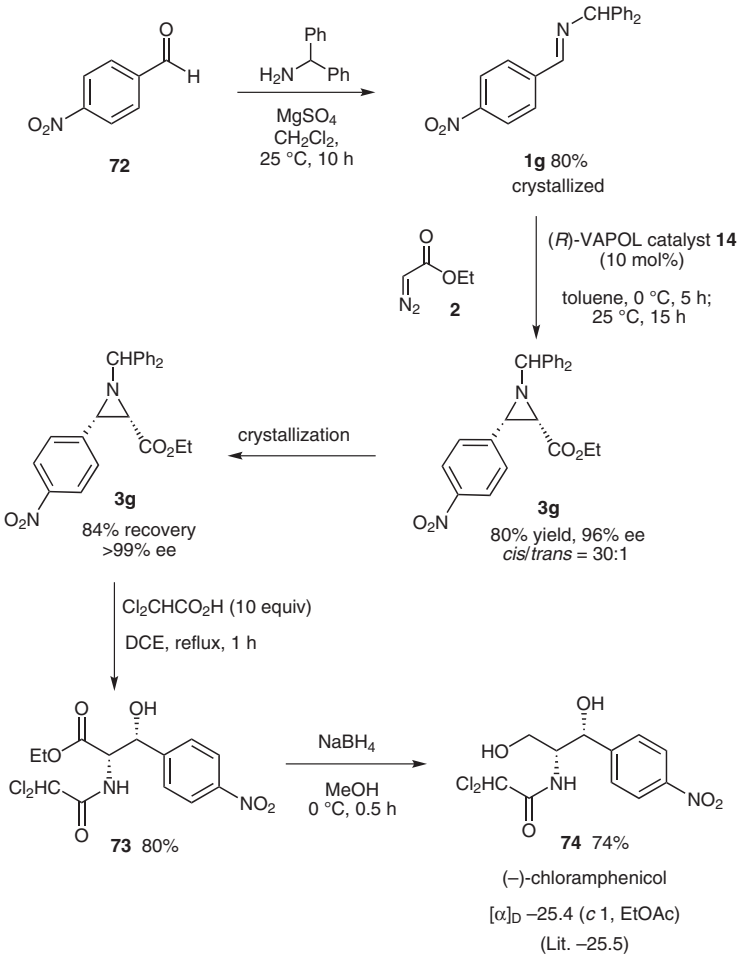
crystallization from hexanes and dichloromethane. Collection of the first crop gave a 72% recovery of material that was optically pure. The tetrasubstituted α-carbon was constructed by the alkylation of aziridine **3c** under the optimized conditions described in Section 3.3 (see Scheme 26) to give a single diastereomer of the methylated aziridine **54h** in 86% yield. The reductive ring opening of **54h** was not as straightforward as it was for the aziridine **3i** (Scheme 27). Treatment of **54h** with palladium on carbon and formic acid resulted in both reductive ring opening at the 3-position as well as reductive cleavage of the bromine. Eventual success was realized with a combination of trifluoroacetic acid and borane–trimethylamine complex, which gave the ring-opened product **67** in 87% yield. Interestingly, attempted ring opening with a combination of trifluoroacetic acid and triethylsilane lead to the formation of the amino alcohol **71** as the major product. Trifluoroacetate is apparently a better nucleophile than triethylsilane in this case. Nonetheless, trifluoroacetic acid/triethylsilane could be used to remove the benzhydryl group from **67**, which gave the amino ester **68** in 95% yield. Completion of the synthesis was straightforward, as shown in Scheme 28, and gave BIRT-377 (**70**) in seven steps from *p*-bromobenzaldehyde.

Chloramphenicol, which was isolated from *Streptomyces venezuelae*, was the first antibiotic to be manufactured synthetically on a large scale and has been in use clinically since 1949. The synthesis of (–)-chloramphenicol (**74**) shown in Scheme 29 utilizes the AZ reaction and is among the shortest asymmetric syntheses, involving only four steps from *p*-nitrobenzaldehyde.[20,39] The key aziridination step utilized the (*R*)-VAPOL catalyst **14** and converted the imine **1g** into aziridine **3g** in 80% yield and 96% ee. Crystallization from hexanes and dichloromethane and collection of the first crop gave optically pure **3g** in 84% recovery. The next step involves a ring opening of the aziridine by an oxygen nucleophile, which under Brønsted acidic conditions generally occurs with inversion (see Scheme 23). When aziridine-2-carboxylate **3g** was subjected to refluxing dichloroacetic acid, a ring-opened α-amino ester **73** was obtained which was then easily reduced to the final product (–)-chloramphenicol (**74**) in 74% yield, as shown in Scheme 29.

The reaction of aziridine **3g** with dichloroacetic acid to give the amino alcohol **73** is a sequence of three reactions (Scheme 30).[20] The first is the ring opening of the protonated aziridine with dichloroacetate which leads to the introduction of the oxygen function in an acylated form to give the structure **76**. In the second step, the benzhydryl group is cleaved from the nitrogen by the dichloroacetic acid to give the free amine **78**. Finally, there is a transacy-



Scheme 29 Synthesis of (–)-chloramphenicol (**74**)

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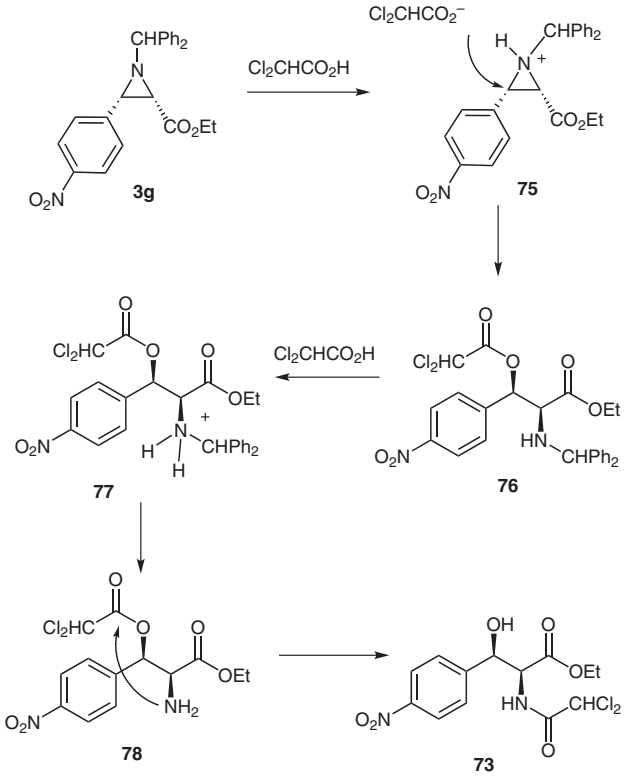

Scheme 30 The ring-opening, deprotection, migration cascade

lation event that results in the migration of the dichloroacetyl group from oxygen to nitrogen.

4 Conclusion and Outlook

The catalytic asymmetric aziridination reaction (AZ reaction) with borate catalysts prepared from the vaulted biaryl ligands VANOL and VAPOL has been developed into a reliable and general method for the asymmetric synthesis of aziridines. These catalysts will effect the transformation of *N*-benzhydryl imines and diazomethyl carbonyl compounds into *cis*-3-substituted aziridine-2-carboxylates (or aziridinyl ketones) with high diastereoselection and enantioselection. Continued development of this AZ reaction in the future will undoubtedly lead to an increased definition of the scope of the reaction with functionalized imines and diazo compounds and to a greater understanding of the mechanism of this asymmetric catalytic process as well as to its increased importance in the field of organic synthesis.

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