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Seeking Passe-Partout in the Catalytic Asymmetric Aziridination of Imines: Evolving Toward Substrate Generality for a Single Chemzyme

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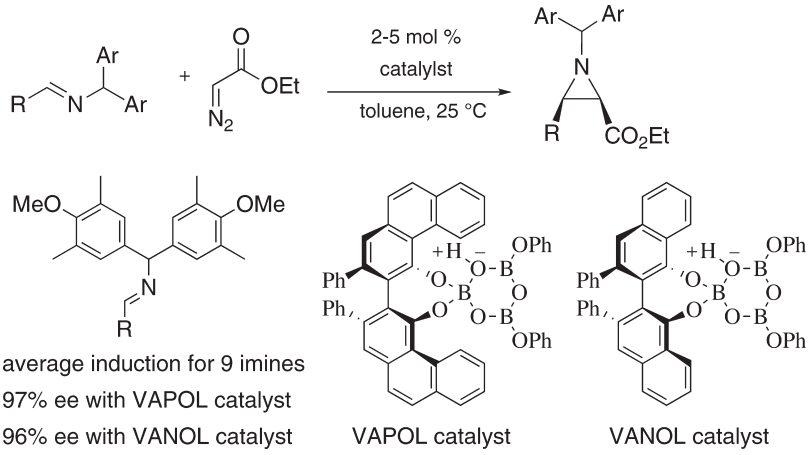

The asymmetric catalytic aziridination reaction (AZ reaction) of imines derived from dianisylmethyl (DAM) amine and tetra-methyldianisylmethyl (MEDAM) amine were examined with boroxinate catalysts prepared from both the VANOL and VAPOL ligands. This included an evaluation of different protocols for the preparation of the catalyst. The AZ reaction of DAM and MEDAM imines prepared from nine different aryl and aliphatic aldehydes were examined. The MEDAM imines were superior to the DAM imines in the AZ reaction, giving much higher asymmetric inductions and higher overall yields of aziridines. The MEDAM imines were found to also be superior to the previously studied diphenylmethyl (benzhydryl or Bh) and tetra-*tert*-butyldianisylmethyl (BUDAM) imines especially for imines derived from aliphatic aldehydes. The average asymmetric induction over the nine different MEDAM imines studied was 97% ee with the VAPOL catalyst and 96% ee with the VANOL catalyst. The MEDAM imines can be deprotected to give *N*-H aziridines in all cases except for some electron-rich aryl aldehydes. The MEDAM imines are much more reactive than benzhydryl imines, and this was most evident when a diazoacetate ester is replaced by a diazoacetamide. The less reactive diazoacetamides give very low yields in their reactions with benzhydryl imines but high yields with MEDAM imines.

Introduction

Aziridines are attractive intermediates in organic synthesis because their ring opening by a variety of nucleophiles under both acidic and basic conditions is facilitated by their ring strain, and the result of this process is normally the stereoselective generation of a β-substituted alkyl amines.[1,2] Although the syntheses of aziridines has been continually honed over the years,[1,2a] the development of catalytic asymmetric methods had lagged behind.[2] Over the past several years we have developed a general method for the catalytic asymmetric synthesis of aziridines that is based on the reaction of diazo compounds with imines and mediated by asymmetric catalysts generated from the VANOL and VAPOL ligands and

(1) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Osborn, H. N. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715. (c) McCoull, W.; Davies, F. A. *Synthesis* **2000**, 1347–1365. (d) Zwanenburg, B.; Holte, P. T. *Top. Curr. Chem.* **2001**, *216*, 93–124. (e) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258. (f) Duban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (g) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743. (h) Mösser, C.; Bolm, C. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2006. (i) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194–206. (j) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979–4988. (k) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135. (l) Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Eur. J. Org. Chem.* **2007**, 1717–1724. (m) Lu, P. *Tetrahedron* **2010**, *66*, 2549.

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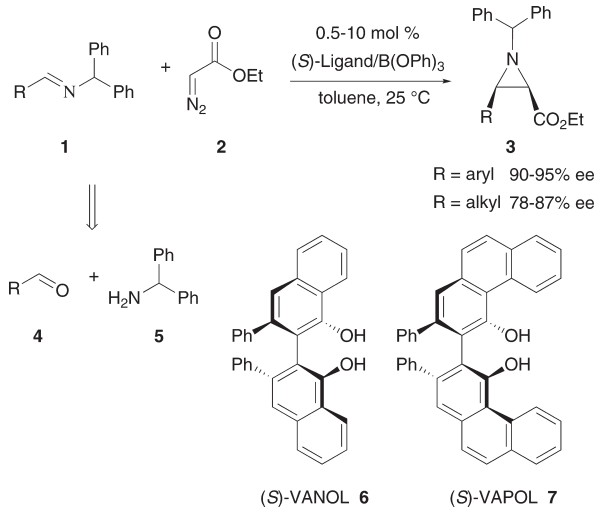
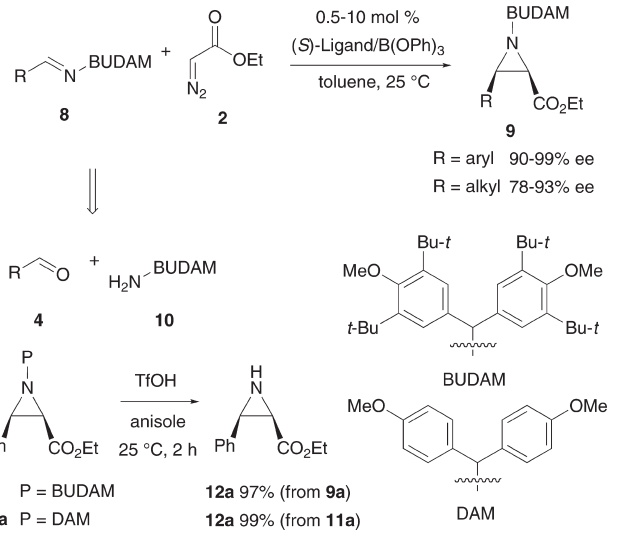
SCHEME 1



SCHEME 2



various boron compounds (Scheme 1).[3−6] Early on it was determined that with imines derived from benzhydryl (Bh) amine **5** and catalysts derived from triphenylborate, aziridines could be obtained in high yields and asymmetric inductions from the reaction of ethyl diazoacetate and other diazo compounds.[3b,e] The reactions are also highly diastereoselective, giving *cis*-2,3-disubstituted aziridines, and in most cases only trace amounts of the *trans*-aziridine can be detected. The scope of the reaction is broad and includes imines derived from a variety of aldehydes including electron-rich and electron-poor aromatic aldehydes and primary, secondary, and tertiary aliphatic aldehydes.[3g] The imines from aromatic aldehydes gave aziridines with 90−95% ee, and imines from aliphatic aldehydes gave aziridines with 77−87% ee.[3g] Interestingly, both VANOL- and VAPOL-derived catalysts are equally effective and give nearly the same asymmetric inductions for each substrate across the entire range of 12 substrates examined.[3g]

More recent studies directed toward mapping the active site of the chemzyme in this reaction have revealed that while the use of a diphenylmethyl group on the imine is essential to the success of this reaction, it does not represent the optimal substituent since it was found that various diarylmethyl groups were far more effective (Scheme 2). A collection of 14 different diarylmethyl substituents was screened for the reaction of imines derived from benzaldehyde, and the optimal selectivity (99% ee) was found for the tetra-*tert*-butyldianisylmethyl (BUDAM) group.[3h] With the identification of the BUDAM substituent as optimal for the imine from benzaldehyde, this substituent was in turn screened with imines prepared from BUDAM amine **10** and 11 different aldehydes. The reactions of BUDAM imines from aromatic aldehydes were definitely superior to their benzhydryl analogues, giving 98−99% ee for most substrates with VAPOL-derived catalysts; however, the reactions of BUDAM imines from aliphatic aldehydes were not significantly different from those with their benzhydryl analogues, giving ee's generally in the 80s. Thus, the goal of the present work is to identify the optimal diarylmethyl substituent that will provide universal access to optically pure aziridines from the AZ reaction irrespective of the substrate.

One of the great advantages of the BUDAM substituent is that it can be easily cleaved under acidic conditions without opening the aziridine ring. For example, the aziridine **9a** (P = BUDAM) can be deprotected to give the *N*-H aziridine **12a** in 97% yield by treatment with 4 equiv of triflic acid in anisole at room temperature for 2 h (Scheme 2).[3h] The corresponding benzhydryl aziridine (**3a**, R = Ph, Scheme 1) leads to ring opening under all acidic conditions that were screened.[3f] The facile cleavage of the BUDAM group under acidic conditions can be attributed to the fact that a significantly more stable diarylmethyl cation is formed during the cleavage. Thus, in seeking the ideal diarylmethyl substituent for the imine, one of the characteristics that would be most desired would be its ability to be removed from the aziridine without causing any deleterious effects to the aziridine. One of the other diarylmethyl groups that was identified in our previous work as superior to the unsubstituted diphenylmethyl (benzhydryl or Bh) group in the AZ reaction is the dianisylmethyl (DAM) group (Scheme 2).[3f] The presence of the methoxyl substituents in the DAM group is sufficient to provide for the clean cleavage of the DAM

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(5) For catalytic asymmetric aziridinations of imines and diazo compounds with other ligands, see: (a) Rasumussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287. (b) Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293. (c) Mayer, M. F.; Hossain, M. M. *J. Organomet. Chem.* **2002**, *654*, 202. (d) Krumper, J. R.; Gerisch, M.; Suh, J. M.; Bergman, R. G.; Tilley, T. D. *J. Org. Chem.* **2003**, *68*, 9705. (e) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987. (f) Wipf, P.; Lyon, A. M. *ARKIVOC* **2007**, *xii*, 91. (g) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380–14381. (h) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445. (i) Zeng, X.; Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036.

(6) For a mechanistically different catalyst with imines and diazo compounds, see: Ranocchiari, M.; Mezzetti, A. *Organometallics* **2009**, *28*, 3611.

CHART 1. Protocols for Catalyst Preparation

Method A

VANOL or VAPOL → (3 equiv $B(OPh)_3$, CH_2Cl_2, 55 °C, 1 h) → (0.1 mm Hg, 55 °C, 0.5 h) → Catalyst

Method B

VANOL or VAPOL → (4 equiv $B(OPh)_3$, 1 equiv H_2O, toluene, 80 °C, 1 h) → (0.1 mm Hg, 80 °C, 0.5 h) → Catalyst

Method C

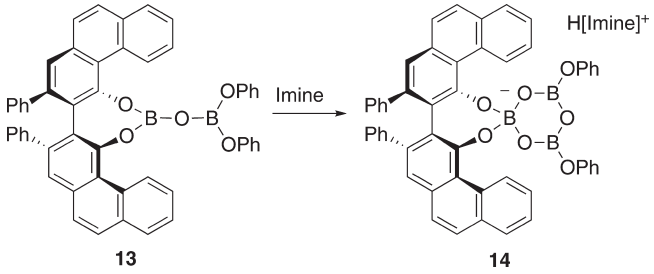
VANOL or VAPOL → (4 equiv $B(OPh)_3$, 33 equiv Imine, toluene, 80 °C, 1 h) → Catalyst

group under acidic conditions, as is illustrated by formation of *N*-H aziridine **12a** in 99% yield from the DAM aziridine **11a** (P = DAM) (Scheme 2). We have previously examined the scope of the aziridination of DAM imines from a variety of aldehydes and found that these imines tend to give slightly improved yields and asymmetric inductions than the corresponding benzhydryl imines.[3f] However, this survey was conducted with methylene chloride and carbon tetrachloride as solvent. Because we have subsequently found that toluene is in many respects superior to either methylene chloride or carbon tetrachloride for the AZ reaction,[3g] we decided to revisit the scope of the AZ reaction of DAM imines.

The protocol for catalyst formation that was used in the previous screen of the AZ reaction of DAM imines[3f] was Method A shown in Chart 1 and is the optimized procedure that was described in the initial report with a catalyst derived from triphenylborate.[3b] It is interesting that the optimized procedure involves 3 equiv of $B(OPh)_3$; at the time it was assumed that the active catalyst involved a 1:1 stoichiometry between the ligand and boron and that the excess $B(OPh)_3$ served to accelerate catalyst formation. Subsequently, it was found that the major species formed under the conditions of Method A was the pyroborate **13** (Scheme 3), which contains one molecule of the ligand and two boron atoms linked by an oxygen.[3g] This prompted an evaluation of the conditions necessary to optimize the formation of the pyroborate species, and the optimal procedure that was found is that indicated in Method B in Chart 1.[3g] Since the formation of a B−O−B linkage requires 1 equiv of water, the use of water as an additive became one of the parameters included in the optimization. Therefore, the study of the AZ reaction of DAM imines in toluene as solvent was begun with a catalyst made by this new protocol prescribed by Method B.

It was during this time that we discovered[3i] that the active catalyst for the AZ reaction was the boroxinate **14**, which contains three boron atoms, thus providing a reason why the

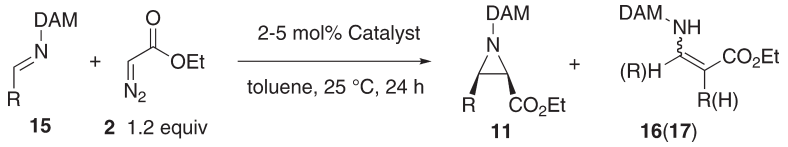
SCHEME 3



13 **14**

original optimized protocol for catalyst formation called for 3 equiv of $B(OPh)_3$.[3b] Furthermore, it was found that the boroxinate **14** is formed by the reaction of the pyroborate **13** with the imine, with or without the presence of an additional 1 equiv of $B(OPh)_3$. In the catalyst protocols indicated in Methods A and B in Chart 1, the exposure to high vacuum at either 55 or 80 °C is not sufficient to remove the third equivalent of $B(OPh)_3$ after the pyroborate **13** is formed, although the phenol produced in the alkoxy exchange between the ligand and $B(OPh)_3$ is removed under either condition. Armed with the knowledge of the catalyst structure, a new protocol for catalyst formation was drawn up and is indicated as Method C in Chart 1; it will be tested for the first time in the present study. The basic aspect of this new method is that the ligand, $B(OPh)_3$, and all of the imine for the reaction (Method C in Chart 1 is indicated for a reaction with 3 mol % catalyst) are heated together in toluene at 80 °C for 1 h, and then upon cooling to room temperature the reaction is initiated by the addition of ethyl diazoacetate. Another significant change in the procedure represented by Method C is that the step involving the removal of volatiles has been deleted. This was done for two reasons: one is our unpublished observation that the presence of phenol does not significantly affect the outcome of the AZ reaction (see Table 5, entry 3 for an example in the present study), and the second is that this greatly simplifies the procedure since removing the solvent at 80 °C under high vacuum sometimes occurs with splattering and loss of catalyst if one is not careful. Finally, it should be noted that the water is left out in Method C. Although the formation of a boroxinate does require 3 equiv of water, studies in the efficiency in the formation of boroxinate **14** by ^1H and ^{11}B NMR revealed that there is sufficient partial hydrolysis in commercial $B(OPh)_3$ to provide the equivalent of three molecules of water.[3i] We have never encountered a bottle of commercial $B(OPh)_3$ that was pure. This fact and the consistency of the impure nature of commercial $B(OPh)_3$ over the years have been responsible for the success and reproducibility of the AZ reaction. The reason that 4 equiv of $B(OPh)_3$ is used in Methods B and C in Chart 1 is to compensate for the fact that $B(OPh)_3$ in not pure as supplied from commercial suppliers. In reality, we have not seen any significant difference in the catalyst prepared with either 3 or 4 equiv of $B(OPh)_3$ either in reaction outcome or in its characterization by ^1H or ^{11}B NMR spectroscopy.[3i] Even with 2 equiv of $B(OPh)_3$ the reaction outcome is not significantly affected. All of this suggests that all of the boron that happens to be present is converted to the boroxinate **14** even if this leaves some of the ligand unreacted, and if any boron is left over, it not does interfere in terms of background reaction.[3i]

TABLE 1. Asymmetric Aziridination with Aryl DAM Imines 15a−g[a]



entry	series	R	ligand	catalyst (mol %)	% yield *cis*-**11**[b]	% ee *cis*-**11**[c]	*cis*:*trans*[d]	% yield **16** (**17**)[e]
1[f]	**a**	Ph	(*R*)-VAPOL	B (5)	95	−92	50:1	1 (1)
2[g]	**a**	Ph	(*S*)-VAPOL	C (3)	90	94	> 50:1	2.7 (2.7)
3	**b**	2-MeC_6H_4	(*S*)-VAPOL	C (3)	70	93	> 50:1	1.4 (1.1)
4	**c**	4-MeC_6H_4	(*S*)-VAPOL	B (5)	90	94	> 50:1	1 (1)
5	**c**	4-MeC_6H_4	(*S*)-VAPOL	C (3)	90	94	> 50:1	1 (1)
6	**d**	4-MeOC_6H_4	(*R*)-VANOL	B (5)	80	−93	> 50:1	2 (1)
7	**d**	4-MeOC_6H_4	(*R*)-VANOL	C (3)	80	−93	50:1	3.2 (1.6)
8[h]	**e**	4-BrC_6H_4	(*S*)-VAPOL	B (3)	94	97	50:1	< 1 (< 1)
9	**e**	4-BrC_6H_4	(*S*)-VAPOL	B (5)	90	97	50:1	< 1 (< 1)
10	**e**	4-BrC_6H_4	(*S*)-VAPOL	B (3)	90	97	50:1	< 1 (< 1)
11[i]	**e**	4-BrC_6H_4	(*S*)-VAPOL	B (2)	87	97	50:1	1 (1)
12	**e**	4-BrC_6H_4	(*S*)-VAPOL	C (3)	89	97	33:1	4.5 (2.7)
13	**f**	4-$NO_2C_6H_4$	(*S*)-VAPOL	B (5)	85	94	33:1	1.6 (1.6)
14	**f**	4-$NO_2C_6H_4$	(*S*)-VAPOL	C (3)	85	95	50:1	< 1 (1 < 1)
15	**g**	1-naphthyl	(*S*)-VAPOL	C (3)	80	98	> 50:1	1.6 (1.6)

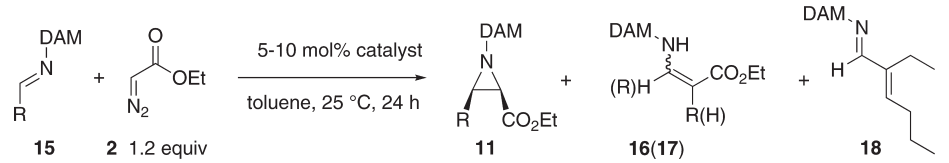
[a]Unless otherwise specified, all reactions went to 100% completion and were performed with catalysts prepared by Methods B or C in Chart 1 with 1.0 mmol of imine **15** and 1.2 equiv of EDA (**2**) at room temperature for 24 h at 0.5 M in **15**. All imines were purified by crystallization. [b]Isolated yield of *cis*-**11** after chromatography on silica gel. [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 ^{1}H NMR spectrum of the crude reaction mixture. [e]Determined by integration of the NH signals of **16** and **17** relative to the methine proton of *cis*-**11** in the ^{1}H NMR spectrum of the crude reaction mixture. [f]A separate reaction with 3 mol % catalyst was complete in 2 h . [g]This reaction was complete in 8 h. [h]Catalyst prepared by Method B in Chart 1 except that water was excluded during the preparation of the catalyst. [i]The reaction was 97% complete.

Results and Discussion

The catalytic asymmetric aziridinations of the DAM imines **15** derived from aromatic aldehydes were screened in toluene with catalysts made with Methods B and C, and the results are presented in Table 1. All of the reactions were carried out for 24 h with 2−5 mol % catalyst, but not all substrates required 24 h to go to completion. The reaction of the phenyl imine **15a** was complete in 2 h with 3 mol % catalyst (Table 1, entry 1). In all cases the reaction went to completion except for entry 11, which went to 97% completion in 24 h with 2 mol % catalyst. The catalyst with VANOL was used for the *p*-methoxyl substrate **15d** since it had been found in our previous studies on DAM imines that this is the slowest substrate and that the VANOL catalyst is approximately twice as fast as the VAPOL catalyst.[3f] One of the clear findings of this study is that, at least for DAM imines derived from aryl aldehydes, there is no difference between Methods B and C for catalyst formation (Chart 1). This is an important observation since Method C is experimentally much more simple a procedure as it does not involve the removal of solvent from the catalyst at high temperature under vacuum. However, the asymmetric inductions do not represent a significant improvement over those previously observed with DAM imines from aryl aldehydes in carbon tetrachloride solvent.[3f] This is not to ignore the fact that toluene is a much more desirable solvent than carbon tetrachloride for reasons of both safety and cost.

At this point we had not yet addressed the critical issue of whether the DAM imines would provide higher inductions for imines from aliphatic aldehydes, since we had only screened the aryl imines shown in Table 1. The aziridinations of the aliphatic DAM imines **15** with a catalyst prepared by Methods B or C from either VANOL or VAPOL were carried out as indicated in Table 2 in toluene at room temperature for 24 h. Considering previous observations that alkyl-substituted imines are generally slower, 5−10 mol % catalyst was used for imines **15h**−**15j**. Unfortunately, the results from the alkyl-substituted DAM imines **15** do not represent an improvement in the asymmetric inductions over those of the corresponding benzhydryl imines **1** and in fact are slightly lower (Table 3). In addition, the aziridination of the primary alkyl-substituted imine **15h** essentially fails in the case of the DAM imine (Table 2, entries 1−4). This reaction produces a very complex mixture with both VANOL and VAPOL catalysts with either Methods B or C and at both room temperature and at 0 °C. A similar complex mixture was produced with DAM imine **15h** in carbon tetrachloride solvent with the VAPOL catalyst prepared from Method A in Chart 1 where the aziridine **11h** was isolated in 11% yield and in 63% ee.[3f] This is to be compared to the corresponding reaction of the benzhydryl imine **1h** (Scheme 1, R = *n*-Pr) prepared from *n*-butanal, which gave the corresponding aziridine **3h** in 40% yield and 81% ee.[3g]The crude ^{1}H NMR spectrum of the reaction of imine **15h** in entries 1−4 in Table 2 reveals the presence of a small amount of aziridine **11h** (6−14%) and small amounts of the unreacted imine **15h** and of the noncyclized enamine products **16h** and **17h**. The only other product as prominent as these in the crude ^{1}H NMR was, after some effort, identified as the vinyl imine **18**, whose structure was confirmed by independent synthesis (see Supporting Information). The compound presumably results from the aldol-type condensation of two molecules of imine **15h**. In contrast, high yields of aziridines were obtained with the secondary and tertiary aliphatic imines **15i** and **15j**, but unfortunately, the asymmetric inductions were not significantly different than those previously observed in carbon tetrachloride.[3f]

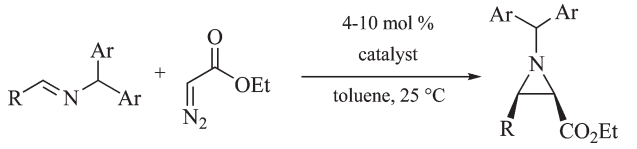
TABLE 2. Asymmetric Aziridination with Alkyl DAM Imines 15h−j[a]



entry	series	R	ligand	catalyst (mol %)	% yield *cis*-**11**[b]	% ee *cis*-**11**[c]	*cis*:*trans*[d]	% yield **16** (**17**)[e]	% yield **18**[f]	% unreacted **15**[f]
1	**h**	*n*-propyl	(*R*)-VANOL	C (10)	nd (6)	nd	nd	3 (1)	7	4
2	**h**	*n*-propyl	(*R*)-VANOL	B (10)	14 (14)	−52	nd	3 (1)	4	2
3[g]	**h**	*n*-propyl	(*S*)-VAPOL	B (10)	11 (11)	73	nd	0 (2)	7	10
4[g]	**h**	*n*-propyl	(*R*)-VANOL	B (10)	10 (10)	−66	nd	2 (1)	8	7
5	**i**	cyclohexyl	(*S*)-VANOL	C (5)	83	82	50:1	< 1 (< 1)	no	0
6[h]	**i**	cyclohexyl	(*R*)-VANOL	B (5)	88	−80	50:1	< 1 (< 1)	no	0
7[i]	**j**	*tert*-butyl	(*S*)-VANOL	C (10)	60	70	20:1	< 1 (< 1)	no	25
8[h]	**j**	*tert*-butyl	(*R*)-VANOL	B (10)	87	−83	50:1	< 1 (< 1)	no	0

[a]Unless otherwise specified, all reactions were performed with 5−10 mol % catalyst prepared by Method B or C with 1.0 mmol of imine and 1.2 equiv of EDA (**2**) in toluene at room temperature for 24 h at 0.5 M in imine. All imines were purified by crystallization except **15h**, which is an oil and was used without purification. nd = not determined. no = not observed. [b]Isolated yield of *cis*-**11** after chromatography on silica gel. Yield in paranthesis are NMR yields with Ph_3CH as internal standard. [c]Determined on purified *cis*-**11** 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 **16** and **17** relative to the methine proton of *cis*-**11** in the ^1H NMR spectrum of the crude reaction mixture. [f]Determined by ^1H NMR with Ph_3CH as internal standard. [g]The reaction was performed at 0 °C for 48 h. [h]The reaction was carried out for 48 h. [i]The reaction was carried out for 55 h.

TABLE 3. Asymmetric Aziridination with Alkyl Imines



Benzhydryl

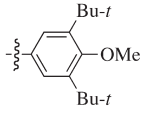
R	Imine	Ligand (mol%)	aziridine	% Yield	% ee
Cy	**1i**	(*S*)-VAPOL (5)	**3i**	73	81
Cy	**1i**	(*R*)-VANOL (5)	**3i**	79	–82
t-Bu	**1j**	(*S*)-VAPOL (5)	**3j**	72	87
t-Bu	**1j**	(*R*)-VANOL (5)	**3j**	89	–85

Ar = 

Method B (ref 3g)

BUDAM

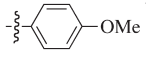
R	Imine	Ligand (mol %)	aziridine	% Yield	% ee
Cy	**8i**	(*S*)-VAPOL (4)	**9i**	89	89
Cy	**8i**	(*S*)-VANOL (4)	**9i**	87	84
t-Bu	**8j**	(*S*)-VAPOL (10)	**9j**	60	78
t-Bu	**8j**	(*S*)-VANOL (10)	**9j**	76	80

Ar = 

Method B (without H_2O, ref 3h)

DAM

R	Imine	Ligand (mol%)	aziridine	% Yield	% ee
Cy	**15i**	(*R*)-VANOL (5)	**11i**	88	–80
t-Bu	**15j**	(*R*)-VANOL (10)	**11j**	87	–83

Ar = 

Method B (this work)

MEDPM

R	Imine	Ligand (mol %)	aziridine	% Yield	% ee
Cy	**19i**	(*S*)-VAPOL (4)	**20i**	87	91
Cy	**19i**	(*S*)-VANOL (4)	**20i**	93	92
t-Bu	**19j**	(*S*)-VAPOL (10)	**20j**	94	96
t-Bu	**19j**	(*S*)-VANOL (10)	**20j**	94	96

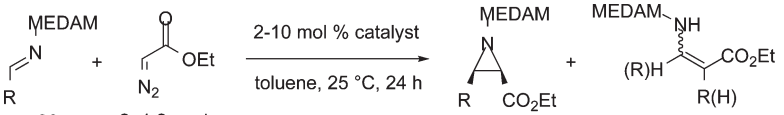
Ar = 

Method B (without H_2O, this work)

Thus our attempts to improve the asymmetric inductions with aliphatic imines by employing the DAM-substituted imines were surceased. A summary of the asymmetric aziridination of the cyclohexyl and *tert*-butyl imines with the benzhydryl, BUDAM, and DAM nitrogen-protecting groups is presented in Table 3. The benzhydryl-substituted imines react to give aziridines **3** in 81−87% ee over both substrates and with catalysts prepared from both the VANOL and VAPOL ligands. The corresponding reactions of the BUDAM imines **8** gave aziridines **9** with inductions in essentially the same range (78−89% ee). The DAM imines give aziridines **11i** and **11j** in 70−82% ee with the VANOL-derived catalyst. In the course of studies directed at mapping both the sterics and electronics of the active site of the catalyst, we had prepared imines generated from tetra-methyldiphenylmethyl (MEDPM) amine.[3h] In a subsequent screen directed at identifying a nitrogen substituent that would lead to higher asymmetric induction for aliphatic imines, we were surprised to find that the imine **19i** from cyclohexane carboxaldehyde and imine **19j** from pivaldehyde both underwent asymmetric aziridination with significantly enhanced inductions when compared to the benzhydryl, BUDAM, and DAM imines (Table 3). Although the dramatic effect of methyl groups in this substituent was not understood, it was nonetheless an important lead in our efforts to identify a substituent on nitrogen that would serve as a master key and allow access to all imines with high asymmetric inductions.

Although the success of the results from the MEDPM imines of aliphatic aldehydes **19i** and **19j** shown in Table 3 served to kindle thoughts of investigating the general scope of the aziridination of these imines, caution was exercised against doing so since our experience told us that it would be difficult to effect acid cleavage of the *N*-protecting group from the aziridines **20**, especially when the substituent R was an aryl group. We had previously established that benzhydryl protecting groups that have *p*-methoxy groups such as BUDAM and DAM can be readily cleaved from aziridines without ring opening (Scheme 2),[3f,h] and thus we then decided to target the preparation of the tetra-methyldianisylmethyl (MEDAM) amine **25b** (Scheme 4) and evaluate the AZ reaction with imines derived therefrom. The MEDAM amine

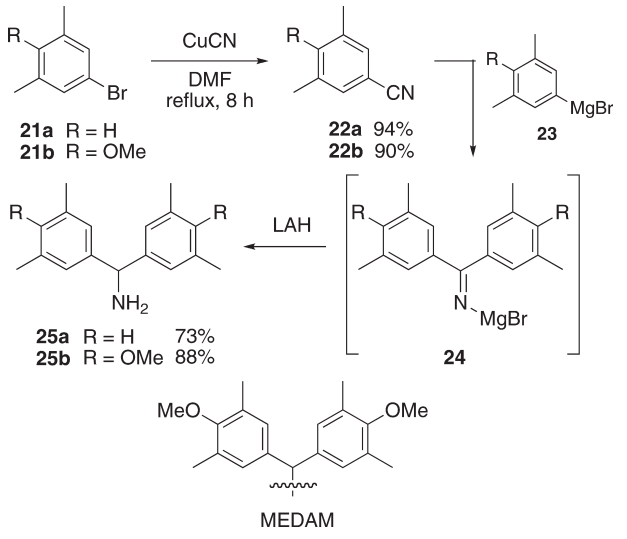
TABLE 4. Asymmetric Aziridination with MEDAM Imine 26 with Method B (with and without H_2O)[a]



entry	imine[b]	R	ligand	catalyst (mol %)	% yield *cis*-**27**[c]	% ee *cis*-**27**[d]	*cis*:*trans*[e]	% yield **28** (**29**)[f]
1	**26a**	Ph	(*S*)-VAPOL	5	98	99.8	> 50:1	2.0 (1.9)
2	**26a**	Ph	(*R*)-VANOL	5	94	−97	> 50:1	2.1 (1.8)
3	**26a**	Ph	(*R*)-BINOL	5	72	−38	17:1	14 (10)
4	**26b**	2-MeC_6H_4	(*S*)-VAPOL	3	91	98	33:1	4.5 (2.7)
5	**26b**	2-MeC_6H_4	(*R*)-VANOL	5	90	−97	50:1	2.7 (2.7)
6	**26c**	4-MeC_6H_4	(*S*)-VAPOL	5	95	99.5	> 50:1	3.8 (0.9)
7	**26c**	4-MeC_6H_4	(*R*)-VANOL	5	94	−97	> 50:1	3.6 (2.7)
8	**26d**	4-$MeOC_6H_4$	(*S*)-VAPOL	3	85	98	50:1	1.0 (1.0)
9	**26d**	4-$MeOC_6H_4$	(*R*)-VANOL	5	83	−96	33:1	3.3 (4.0)
10[g]	**26e**	4-BrC_6H_4	(*S*)-VAPOL	2	89	99.5	> 50:1	1.0 (1.0)
11	**26e**	4-BrC_6H_4	(*S*)-VAPOL	3	95	99.6	> 50:1	2.0 (1.9)
12	**26e**	4-BrC_6H_4	(*S*)-VAPOL	5	97	99.5	> 50:1	1.0 (1.0)
13	**26e**	4-BrC_6H_4	(*R*)-VANOL	5	95	−97	> 50:1	1.2 (1.4)
14	**26f**	4-$NO_2C_6H_4$	(*S*)-VAPOL	5	96	99.7	> 50:1	1.2 (2.0)
15	**26f**	4-$NO_2C_6H_4$	(*R*)-VANOL	5	95	−97	> 50:1	0 (1.9)
16	**26k**	*n*-hexyl	(*S*)-VAPOL	3	67	90	nd	nd
17	**26h**	*n*-propyl	(*S*)-VAPOL	10	64	93	nd	15.3 (8.3)
18[h]	**26h**	*n*-propyl	(*S*)-VAPOL	10	72	97	nd	3.0 (1.5)
19	**26h**	*n*-propyl	(*R*)-VANOL	10	73	−94	nd	0 (1.5)
20[h]	**26h**	*n*-propyl	(*R*)-VANOL	10	75	−95	nd	0 (0)
21[h,i]	**8h**	*n*-propyl	(*S*)-VAPOL	10	69	95	nd	10.3(4.4)
22[h,i]	**8h**	*n*-propyl	(*R*)-VANOL	10	75	−93	nd	nd (5.3)
23	**26i**	cyclohexyl	(*S*)-VAPOL	3	98	91	> 50:1	nd
24[h]	**26i**	cyclohexyl	(*S*)-VAPOL	3	94	91	nd	0(3)
25	**26i**	cyclohexyl	(*R*)-VANOL	3	95	−91	> 50:1	nd
26	**26j**	*tert*-butyl	(*S*)-VAPOL	3	95	94	> 50:1	nd
27	**26j**	*tert*-butyl	(*R*)-VANOL	3	97	−96	> 50:1	nd
28[h]	**26j**	*tert*-butyl	(*R*)-VANOL	10	95	−96	nd	0(3)

[a]For all reactions with 2 and 3 mol % catalyst, the catalyst was prepared by Method B in Chart 1 except that water was excluded during catalyst preparation. For all reactions with 5 and 10 mol % catalyst, the catalyst was prepared by Method B in Chart 1. Unless otherwise specified, all reactions were carried out with 1.0 mmol of **26** at 0.5 M in toluene with 1.2 equiv of **2** at 25 °C and went to completion in 24 h. [b]All imines were purified by crystallization except **26h**, **26k**, and **8h**, which were oils and were used without purification. Imine **26k** was prepared by method 1, and **26h** and **8h** were prepared by method 2 given in Supporting Information. [c]Isolated yield of *cis*-**27** after chromatography on silica gel. [d]Determined on purified *cis*-**27** by HPLC on a CHIRAL CEL OD-H column. [e]Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of the crude reaction mixture. nd = not determined. [f]Determined by integration of the NH signals of **28** and **29** relative to the methine proton of *cis*-**27** in the ^{1}H NMR spectrum of the crude reaction mixture. [g]Reaction was 97% complete. [h]Reaction performed at 0 °C for 24 h. [i]Imine prepared from BUDAM amine **10**; product is aziridine **9h**.

SCHEME 4

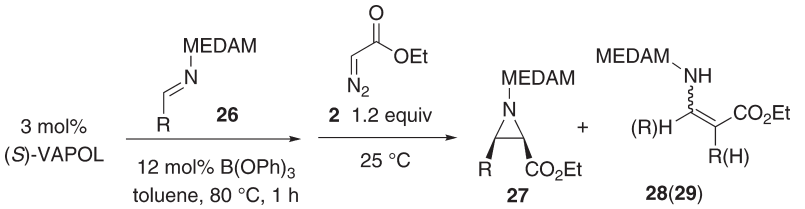


25b can be prepared in one step from the commercially available 4-bromo-2,6-dimethylanisole **21b** and the commercially available nitrile **22b**.[7] Alternatively, the nitrile **22b** can be prepared from the bromide **21b** by the Shechter modification of the Rosenmund−Van Braun reaction.[8] The key step then involves the reaction of the nitrile **22b** with the Grignard reagent generated from the bromide **21b** and in situ reduction of the resulting adduct **24** to provide the amine **25b** in 88% yield from the nitrile **22b**.

The scope of the AZ reactions of the 10 MEDAM imines **26** shown in Table 4 were performed in toluene at room temperature with both VANOL and VAPOL catalysts (2−10 mol %) prepared by Method B (with or without H_2O). Of the MEDAM imines prepared from aryl aldehydes, four out of six give 99% ee for the aziridine **27** with the VAPOL catalyst and the other two give 98% ee. This level of asymmetric induction rivals that observed for BUDAM imines of aromatic aldehydes,[3h] and likewise, both imines give slightly lower inductions (∼97% ee) with the VANOL catalyst. Another important feature that the MEDAM imines have in common with the BUDAM imines is that they both give high

(7) Alternatively, bromide **21b** can be made from the inexpensive 2,6-dimethylphenol; see Supporting Information.
(8) Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522.

TABLE 5. Asymmetric Aziridination with MEDAM Imine 26 with Method C[a]



entry	imine[b]	R	time (h)	% yield *cis*-**27**[c]	% ee *cis*-**27**[d]	*cis*:*trans*[e]	% yield **28** (**29**)[f]
1[g]	**26a**	Ph	3	94	99	> 50:1	3.8 (1.9)
2	**26a**	Ph	0.25	93	98.5	> 50:1	2.5 (2.0)
3[h]	**26a**	Ph	24	94	95.5	50:1	2.8 (2.8)
4[i]	**26a**	Ph	24	≤15	nd	nd	nd
5[j]	**26b**	2-MeC_6H_4	24	87	96	33:1	5.0 (3.2)
6	**26c**	4-MeC_6H_4	0.5	94	99	> 50:1	3.0 (1.2)
7[k]	**26d**	4-$MeOC_6H_4$	24	83	97	50:1	1.2 (2.1)
8	**26e**	4-BrC_6H_4	2	94	99	> 50:1	1.5 (1.9)
9	**26f**	4-$NO_2C_6H_4$	0.75	95	99	> 50:1	1.2 (2.0)
10[l]	**26k**	*n*-hexyl	24	64	86	nd	10 (0)
11	**26i**	cyclohexyl	3	96	89	50:1	nd
12[m]	**26j**	*tert*-butyl	24	93	92	50:1	nd

[a]Unless otherwise specified, all reactions went to completion and were performed with 3 mol % catalyst prepared (Method C) by heating 3 mol % of (*S*)-VAPOL with 12 mol % $B(OPh)_3$ and 1 mmol of imine **26** as a 0.5 M solution in toluene at 80 °C for 1 h. The flask was cooled to room temperature, and then 1.2 equiv of EDA (**2**) was added, and the mixture stirred for indicated time. nd = not determined. [b]All imines were purified by crystallization except **26k**, which was an oil and was used without purification. Imine **26k** was prepared by method 1 described in Supporting Information. [c]Isolated yield after column chromatography on silica gel. [d]Determined on purified *cis*-**27** by HPLC on a CHIRAL CEL OD-H column. [e]Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^1H NMR spectrum of the crude reaction mixture. [f]Determined by integration of the NH signals of **28** and **29** relative to the methine proton of *cis*-**27** in the ^1H NMR spectrum of the crude reaction mixture. [g]A separate reaction with 1 mol % catalyst and 5 mmol of **26a** that went to 67% completion in 0.5 h. [h]100 mol % PhOH was added just prior to EDA (**2**). Minimum reaction time not determined, but the reaction did go to completion in 24 h. [i]100 mol % H_2O was added just prior to EDA (**2**). Reaction only went to 15% completion in 24 h. No further purification was carried out. [j]94% complete after 12 h. [k]Reaction went to 97% completion. [l]Reaction went to only 87% completion. [m]20% complete after 2 h, 44% complete after 8 h, and 98% complete after 24 h.

cis-selectivity with *ortho*-substituted aryl imines. Specifically, both give high selectivity for the *cis*-aziridine with imines prepared from *o*-methylbenzaldehyde (Table 4, entry 4 and 5). This is in contrast to the corresponding benzhydryl imine **1b** (Scheme 1, R = 2-MeC_6H_4), which gives a 10:1 mixture of *cis* and *trans* aziridines.[3g] Most importantly, the high asymmetric inductions observed in the screen with the MEDPM imines **19** with aliphatic aldehydes (Table 3) are maintained and are essentially identical to those observed for the corresponding MEDAM imines **26** (Table 4, entries 23−28 vs Table 3, entries 11−14). The asymmetric induction could not be improved by lowering the temperature to 0 °C for either the cyclohexyl or *tert*-butyl substrates (entries 24 and 28). Most importantly, the use of the MEDAM activating group allows for the efficient asymmetric aziridination of imines with primary aliphatic substituents (entries 16−22). In this case, the asymmetric induction could be slightly increased by lowering the temperature to 0 °C as is illustrated by the isolation of the aziridine **27h** in 72% yield and 97% ee (entry 18). A slightly lower result was observed for the BUDAM imine **8h** at this temperature (entry 21). The asymmetric induction observed for the catalyst prepared from (*R*)-BINOL was examined for the reaction of the phenyl imine **26a** (entry 3). The asymmetric induction of 38% ee with the MEDAM imine **26a** for the BINOL catalyst is to be compared with 67% ee with the BUDAM imine **8a** (R = Ph)[3h] and 20% ee with the benzhydryl imine **1a** (R = Ph).[3b]

The results of the evaluation of the catalytic asymmetric aziridinations of MEDAM imines summarized in Table 4 reveal that VAPOL ligand gives slightly higher asymmetric inductions than does the VANOL ligand. The catalyst generated from the VAPOL ligand was re-evaluated for the MEDAM imines with the catalyst preparation procedure indicated by Method C in Chart 1 since this procedure is experimentally far easier to perform, and the results are given in Table 5. As was the case with the DAM imines (Tables 1 vs 2), there was very little difference between the two procedures, and thus Method C becomes the protocol of choice for the AZ reaction. As was the case with Method B, the aziridination of MEDAM imines generated from aryl aldehydes with a VAPOL catalyst Method C gives aziridines **27** in 99% ee for four out of the six aryl imines and the other two give aziridines in 96% and 97% ee. It is to be noted that the asymmetric inductions for the MEDAM imines of aliphatic aldehydes dropped off slightly (2−4% ee) with Method C (Table 5) compared to Method B (Table 4), but they are nonetheless superior to any of the other diaryl methyl amine groups we have examined including DAM, BUDAM, and benzhydryl groups. The minimum reaction times for all nine MEDAM imine substrates in Table 5 were determined for reactions with 3 mol % catalyst. The reactions of the aryl imines were complete within 15−120 min with the exception of the *p*-methoxyphenyl imine **26d**, which required 24 h to go to 97% completion (entry 7). The secondary and tertiary alkyl-substituted imines **26i** and **26j** were in general slower than the aryl imines, requiring 3−24 h to reach completion. The reaction of the *n*-hexyl-substituted imine **26k** was 87% complete in 24 h. Finally the effect of added water and phenol on the reactions of the MEDAM imines was examined. The addition of 100 mol % water to the reaction just prior to the addition of ethyl diazoacetate essentially stops the reaction of the phenyl imine **26a** since it went to only 15%

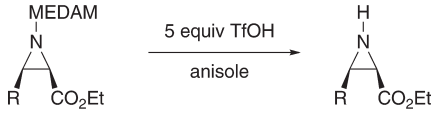
completion in 24 h (Table 5, entry 4). On the other hand, the presence of phenol has only a small effect on the reaction. The addition of 100 mol % phenol does not effect the yield of the reaction and leads to only a slight drop in the asymmetric induction (Table 5, entry 3); this reaction was allowed to run for 24 h, and no attempt was made to determine the minimum reaction time. This suggests that the removal of the volatiles including phenol in Methods A and B for catalyst formation does not have a significant beneficial effect on the AZ reaction.

The removal of the MEDAM group from the nitrogen in the aziridines **27** to give the *N*-H aziridines **12** will be an important aspect of the chemistry of MEDAM aziridines that will serve to facilitate their application in synthesis.[1,2] This is especially true in those transformations that involve nucleophilic opening of the aziridine under basic conditions, since this type of reaction usually requires an electron-withdrawing group on the nitrogen. The protocol for cleavage involves treatment with 5 equiv of triflic acid in anisole and is based on that developed for the deprotection of DAM aziridines.[3f] We were pleased to see that the cleavage of the phenyl-substituted MEDAM aziridine **27a** proceeded under this standard procedure to give the *N*-H aziridine **12a** in 95% yield. It was anticipated that deprotection of the electron-rich *p*-methoxyphenyl aziridine **27d** would be problematic since this was the case with the corresponding DAM aziridine.[3f] Indeed attempted deprotection of **27d** led to a mixture of many products including ring-opening adducts with anisole. This was also found to be the case with the *p*-methylphenyl aziridine **27c**, although interestingly, the deprotection of the 2-methyl substituted aziridine **27b** proceeded smoothly to give aziridine **12b** in 97% yield. It is possible that aziridines **27c** and **27d** could be deprotected by the ozonolysis method we have previously reported for benzhydryl aziridines, although this was not tested.[9] The deprotection of the other aryl aziridines all occurred in yields of at least 95%. The deprotection of the alkyl-substituted aziridines was slower than that of the aryl aziridines and required heating to 65 °C for short periods of time but nonetheless gave good to excellent yields of the aziridines **12h**−**12j** (Table 6, entries 7−9).

In addition to the finding that the MEDAM protecting group provides the highest asymmetric inductions over the broadest range of substrates for the catalytic asymmetric aziridination of imines for any protecting group we have screened to date, the MEDAM group on the imine was also found to be the best group for asymmetric aziridinations with the diazoacetamide **30**. This diazoacetamide was examined in a view to develop an efficient method for the synthesis of the natural product amathaspiramide F.[10] The benzhydryl group was initially examined and was found to be very slow in its reaction with diazoacetamide **30** (Table 7). Employing 10 mol % of the VANOL-$B(OPh)_3$-derived catalyst, the reaction of imine **1a** with **30** gave only a 16% yield of *cis*-aziridine **31a** in 77% ee after 24 h (entry 1).[11] Switching to the VAPOL-derived catalyst led to an enhancement of the asymmetric induction to 88% ee (entry 2). Increasing the reaction time to 64 h and at the same time increasing the catalyst loading to 20 mol % did not change the outcome (entry 3). One explanation for the sluggishness of these reactions is that there is product inhibition of the catalyst. Thus, we decided to examine the effect of added $B(OPh)_3$ on this reaction since this had proved to be effective in ameliorating the product inhibition in a heteroatom Diels−Alder reaction with the same catalyst.[12] Although there is essentially no background reaction with $B(OPh)_3$ (entry 7), the addition of 200 mol % of $B(OPh)_3$ did not change the yield of the reaction in either CCl_4 or in toluene (entries 4 and 5), suggesting that if product inhibition is the problem, $B(OPh)_3$ is not successfully completing for binding with the product. The reaction of the BUDAM imine **8a** with diazoacetate **30** gives improved yield in the aziridination with diazoacetamide **30** producing **32a** in 40% yield after 24 h with 10 mol % catalyst and also gave slightly higher induction (entry 8). The MEDPM imine **19a** was even more effective, giving a 66% yield and 97% ee under the same conditions (entry 9). The reaction of the MEDAM imine **26a** is comparable, giving a 60% yield of aziridine **34a** in 24 h and in 96% ee (entry 10). This reaction only went to 68% completion, but if the amount of catalyst is raised to 20 mol %, the reaction does go to completion and gives aziridine **34a** in 77% yield and 98% ee (entry 11).

The asymmetric inductions for the catalytic asymmetric aziridination with the VANOL-derived catalyst are plotted in Chart 2 for nine different substrates against the four different *N*-substituents. This are a compilation of results with the inductions for the benzhydryl imines[3g] and BUDAM imines[3h] taken from previous publications and from the present work for the DAM and MEDAM imines (see Table S1 in Supporting Information for details on the data in Chart 2). It is clear from Chart 2 that for imines derived from the indicated six aryl aldehydes the BUDAM and MEDAM imines are both superior substrates when compared with the DAM and benzhydryl (Bh) imines. The former give an average of 98% ee and 97% ee, respectively, over the six aryl substituents, whereas the later both give an

TABLE 6. Deprotection of MEDAM Aziridines 27[a]



27 **12**

entry	aziridine	R	time (h)	temp (°C)	% yield **12**[b]
1	**27a**	Ph	2	25	95
2	**27b**	2-MeC_6H_4	1	25	97
3	**27c**	4-MeC_6H_4	1	25	*c*
4	**27d**	4-$MeOC_6H_4$	1	25	*c*
5	**27e**	4-BrC_6H_4	1	25	96
6	**27f**	4-$NO_2C_6H_4$	1	25	97
7	**27h**	*n*-propyl	1	65	72[d]
8	**27i**	cyclohexyl	0.5	65	90
9	**27j**	*tert*-butyl	0.7	65	88

[a]0.15 M in **27**. [b]Isolated yield after chromatography on silica gel. [c]Mixtures of products observed including ring-opened products. [d]The yield of this reaction by ^1H NMR was 76% with Ph_3CH as internal standard.

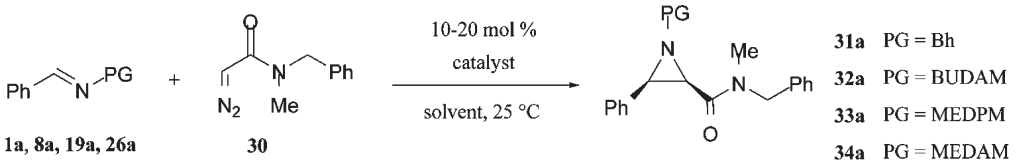
(9) Patwardhan, A. P.; Lu, Z.; Pulgam, V. R.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 2201–2204.

(10) Blackman, A. J.; Green, R. D. *Aust. J. Chem.* **1987**, *40*, 1655.

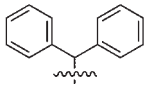
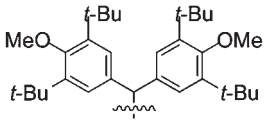
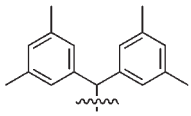
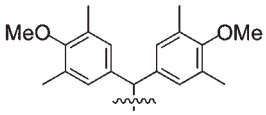
(11) The reactions of imines with secondary diazoacetamides have been reported to give trans aziridines: see refs 5g and 5i.

(12) Newman, C. A.; Antilla, J. C.; Chen, P.; Predeus, A.; Fielding, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7216–7217.

TABLE 7. Comparison of Various Imines in Aziridination with Diazoacetamide 30[a]



1a, 8a, 19a, 26a — 30

entry	imine	PG	ligand (mol%)	mol% $B(OPh)_3$	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**		(*R*)-VANOL (10%)	30	CCl_4	64	16	–77
2[d]	**1a**		(*S*)-VAPOL (10%)	30	CCl_4	24	14	88
3[d]	**1a**		(*S*)-VAPOL (20%)	60	CCl_4	64	18	88
4	**1a**		(*S*)-VAPOL (10%)	200	CCl_4	40	16	85
5	**1a**		(*S*)-VAPOL (10%)	200	toluene	40	18	88
6	**1a**		(*S*)-VAPOL (100%)	300	CCl_4	24	5	nd
7[e]	**1a**		none	200	CCl_4	24	nd	nd
8[f]	**8a**		(*S*)-VAPOL (10%)	40	toluene	24	40	93
9[g]	**19a**		(*S*)-VAPOL (10%)	40	toluene	24	66	97
10[h]	**26a**		(*R*)-VAPOL (10%)	40	toluene	24	60	–96
11[i]	**26a**		(*S*)-VAPOL (20%)	80	toluene	24	77	98

[a]Unless otherwise specified, all reactions were carried out at 0.5 M in imine with 1.05 equiv of **30** with a catalyst prepared by Method B unless otherwise specified in Supporting Information The reactions in the first six entries all went to less than 50% completion. nd = not determined. [b]Isolated yield after silica gel chromatography. [c]Determined by HPLC on a Chiracel OD-H column. [d]Diazo amide **30** added slowly over 5 h by syringe pump. [e]This reaction went to < 5% completion. [f]This reaction went to 42% completion. [g]This reaction went to 70% completion. [h]This reaction went to 68% completion. [i]This reaction went to 100% completion.

average of 91% ee over the same six substrates. The situation is different for the three imines derived from aliphatic aldehydes. The MEDAM imines give a much higher asymmetric induction for the aliphatic substituents than do the BUDAM, DAM, or benzhydryl imines. The MEDAM imines give an average of 94% ee for the three aliphatic imines, whereas the BUDAM, DAM, and benzhydryl imines give 87%, 76%, and 83% ee, respectively (Table S3 in Supporting Information).

The results of asymmetric inductions for the catalytic asymmetric aziridination with the VAPOL-derived catalyst are plotted in Chart 3 for nine different substrates against the four different *N*-substituents. As was the case for the data from the VANOL catalyst shown in Chart 2, the inductions for the benzhydryl imines[3g] and BUDAM imines[3h] were taken from data in previous publications and from the present work for the DAM and MEDAM imines (see Table S2 in Supporting Information for details on the data in Chart 3). The trends seen for the VAPOL ligand are very similar to those observed for the VANOL ligand. For the six aromatic substrates, MEDAM and BUDAM imines give the highest inductions with an average of 99% ee and 98% ee, respectively. The benzhydryl (Bh) and DAM imines give lower average inductions of 89% ee and 94% ee, respectively. For the three aliphatic imines, the MEDAM substituent was clearly the most effective giving 94% ee averaged over the primary, secondary, and tertiary aliphatic imines, which coincidentally was the same average observed for the VANOL catalyst over the same substrates. The other *N*-substituents were not nearly as effective with average inductions of 85% ee for benzhydryl imines, 79% ee for the DAM imines, and 87% ee for the BUDAM imines (Table S3 in Supporting Information).

Given the difference in size of the VANOL and VAPOL ligands, it is quite remarkable that these ligands give nearly identical asymmetric inductions over all nine substrates shown in Charts 2 and 3 and over all four different protecting groups on the imine (for numerical averages for yields and % ee, see Table S3 in Supporting Information). For the BUDAM and MEDAM imines, the VAPOL ligand gives only slightly higher inductions on average (1% ee averaged over nine substrates for each imine) and thus in the absence of any other factors would be the ligand of choice for this reaction. Considerations in favor of choosing the VANOL ligand is the fact that its molecular weight is approximately 20% less than that VAPOL, thus requiring less ligand per reaction at

CHART 2. Distribution of Asymmetric Induction with Protecting Group for the VANOL Catalyst

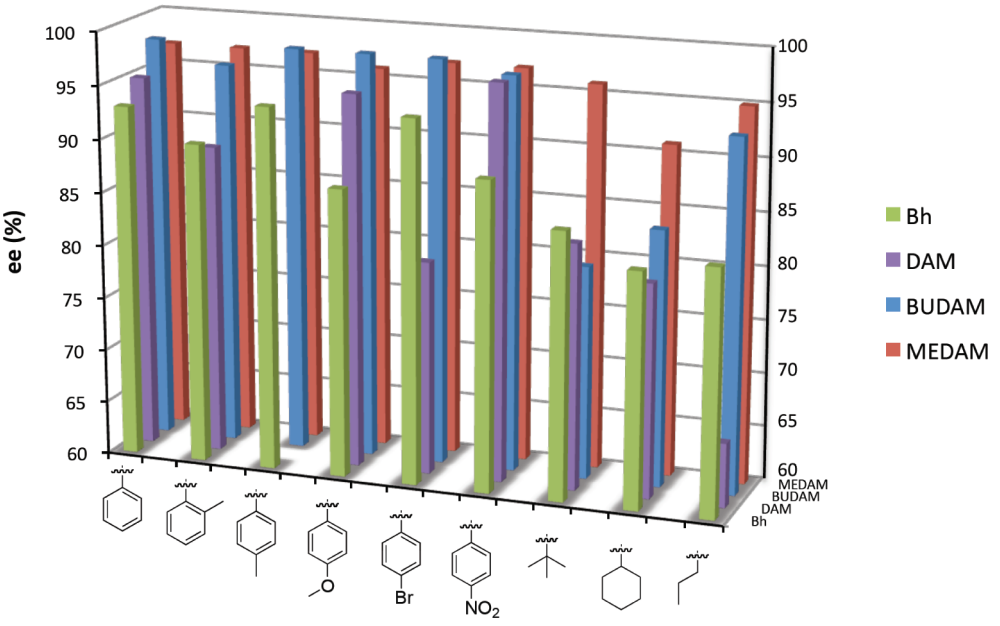
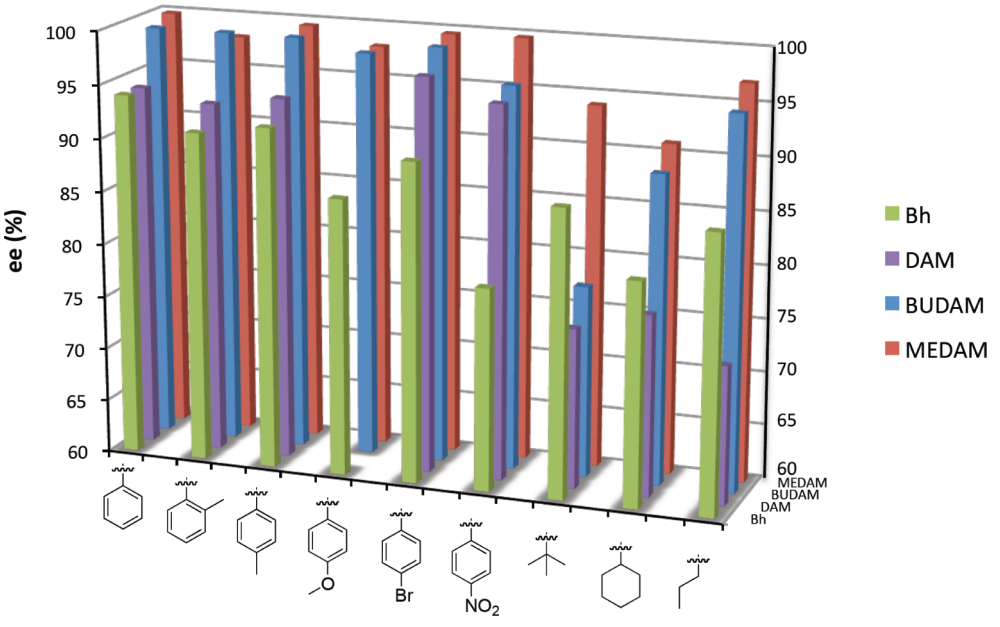


CHART 3. Distribution of Asymmetric Induction with Protecting Group for the VAPOL Catalyst



least by weight. In addition, less ligand by mole percentage has also been observed for the VANOL ligand. In side by side comparisons, catalyst loading studies revealed that aziridination of the benzhydryl imine derived from *p*-bromobenzaldehyde could be brought to complete conversion at 0.5 mol % loading with the VANOL catalyst, whereas complete conversion with the VAPOL catalyst required 1.0 mol % loading.[13] This may be related to a finding in a competition study that the VANOL catalyst is two times faster than the VAPOL catalyst.[3f]

The results of these studies have shown that the MEDAM substituent is clearly the N-substituent of choice for the catalytic asymmetric aziridination of imines with ethyl diazoacetate. The aziridines **27** are obtained in very high asymmetric inductions and *cis*-selectivities over a range of MEDAM imines derived from both aromatic and aliphatic aldehydes. The BUDAM and MEDAM imines give similar inductions for aryl imines, but the MEDAM imines are superior for aliphatic imines. The benzhydryl imines give significantly lower yields and lower inductions than the MEDAM imines (Table S3 in Supporting Information), but the benzhydryl aziridines are often crystalline and their optical purity can be enhanced in most cases to >99% ee by crystallization.[3g] Thus, the benzhydryl group may be the N-substituent of choice since the benzhydryl amine is commercially available and the MEDAM amine is not, although it can be

(13) Desai, A.; Morán-Ramallal, R.; Wulff, W. D., *Org. Synth.*, submitted for publication.

made in a single step from commercially available materials. Nonetheless, there are fundamental limitations of the benzhydryl imines that can be addressed by the use of MEDAM imines in the AZ reaction. The synthesis of aziridines that are not crystalline will undoubtedly be most attractive with methods that give the highest asymmetric inductions of products directly from the reaction. Also, the benzhydryl group cannot be removed from the aziridine in an efficient manner to give N−H aziridines if the imine is derived from an aryl aldehyde. This would be important in utilizing any of the many ring-opening reactions of aziridines that require an electron-withdrawing group on the nitrogen. Finally, the MEDAM substituent is serving as not only a selectivity auxiliary in the AZ reaction but also an activating group. The rates of the aziridination reaction are much faster with MEDAM imines compared to benzhydryl imines. In a competition experiment, it was found that the MEDAM imine from benzaldehyde reacted 11.5 times faster than the corresponding benzhydryl imine.[3h]

Experimental Section

General Information. All reactions were carried out in flame-dried glassware under an atmosphere of argon unless otherwise indicated. Triethylamine, dichloromethane, and acetonitrile were distilled over calcium hydride under nitrogen. Tetrahydrofuran, dioxane, and ether were distilled from sodium and benzophenone. Toluene was distilled from sodium under nitrogen. All reagents were purified by simple distillation or crystallization with simple solvents unless otherwise indicated. Ethyl diazoacetate **2** and triphenylborate were obtained from Aldrich Chemical Co., Inc. and used as received. VAPOL and VANOL were made according to published procedure.[14] The preparations of the DAM imines **15** and the MEDAM imines **26** are given in Supporting Information, as are the syntheses of the DAM aziridines **11** and the diazoacetamide **30**.

General Procedure for the Synthesis of MEDAM Aziridines 27 and BUDAM Aziridine 9h via Method B, Illustrated for Aziridines 27a, 27h, and 9h. (2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 27a. To a 25 mL flame-dried homemade Schlenk flask (see Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VAPOL (27 mg, 0.05 mmol) and $B(OPh)_3$ (58 mg, 0.2 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents, and this was followed by the addition of water (0.9 μL, 0.05 mmol). The flask was sealed by closing the Teflon valve and then placed in an 80 °C (oil bath) for 1 h. After 1 h, a vacuum (0.5 mmHg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 °C (oil bath). The flask was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask.

To the flask containing the catalyst were added first the aldimine **26a** (387 mg, 1 mmol) and then dry toluene (2 mL) under an argon flow through side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light orange solution. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow toward the completion of the reaction. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 1 h to afford the crude aziridine as an off-white solid.

A measure of the extent to which the reaction went to completion was estimated from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the proton on the imine carbon. The *cis*:*trans* ratio was determined by comparing the ^{1}H NMR integration of the ring methine protons for each aziridine in the crude reaction mixture. The *cis* (J = 7−8 Hz) and the *trans* (J = 2−3 Hz) coupling constants were used to differentiate the two isomers. The yields of the acyclic enamine side products **28a** and **29a** were determined by ^{1}H NMR analysis of the crude reaction mixture by integration of the *N*-H proton relative to the that of the *cis*-aziridine methine protons with the aid of the isolated yield of the *cis*-aziridine. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure aziridine **27a** as a white solid (mp 107−108 °C on 99.8% ee material) in 98% isolated yield (396 mg, 0.98 mmol); *cis*:*trans* > 50:1. Enamine side products: 2% yield of **28a** and 1.9% yield of **29a**. The optical purity of **27a** was determined to be 99.8% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.26 min (major enantiomer, **27a**) and t_R = 12.52 min (minor enantiomer, *ent*-**27a**). The AZ reaction of imine **26a** with (*R*)-VANOL gave *ent*-**27a** in 94% yield with 97% ee and *cis*:*trans* of > 50:1. Performing the reaction with (*R*)-BINOL gave *ent*-**27a** in 72% yield with 38% ee and *cis*:*trans* of > 17:1. Spectral data for **27a**:[3] R_f = 0.42 (1:9 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, 3H, J = 7.1 Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.55 (d, 1H, J = 6.8 Hz), 3.10 (d, 1H, J = 6.6 Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H) 3.87−3.97 (m, 2H), 7.09 (s, 2H), 7.18 (s, 2H), 7.21−7.24 (m, 3H), 7.36 (d, 2H, J = 7.3 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.0, 16.2, 16.2, 46.3, 48.2, 59.5, 59.6, 60.5, 77.0, 127.2, 127.4, 127.7, 127.8, 127.9, 130.6, 130.6, 135.3, 137.8, 138.0, 156.0, 156.1, 168.0; IR (thin film) 2961 vs, 1750 vs, 1414 vs, 1202 vs cm^{-1}; mass spectrum m/z (% rel intensity) 473 M+ (0.27), 284(78), 283 (100), 268 (34), 253 (20), 237 (11), 210(10), 117 (18), 89 (11). Anal. Calcd for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 76.31; H, 7.28; N, 2.82. $[\alpha]^{23}_D$ +41.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[3h]

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-propylaziridine-2-carboxylate 27h. The imine **26h** was an oil and was generated and used in situ. To a 10 mL flame-dried round-bottom flask filled with argon were added bis(4-methoxy-3,5-dimethylphenyl)methanamine **25b** (299 mg, 1 mmol), 4 Å MS (250 mg, freshly dried), and dry toluene (1.5 mL). After stirring for 10 min, butanal **4h** (78 mg, 1.05 mmol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 3 h. The resulting imine **26h** was used without further purification. Spectral data for **26h**: ^{1}H NMR ($CDCl_3$ 500 MHz) δ 0.94 (t, 3H, J = 7.3 Hz), 1.58 (sextet, 2H, J = 7.3 Hz), 2.23 (s, 12H), 2.28−2.32 (m, 2H), 3.67 (s, 6H), 5.09 (s, 1H), 6.92 (s, 4H), 7.75 (t, 1H, J = 4.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 16.2, 19.5, 37.8, 59.6, 77.7, 127.8, 130.6, 139.2, 155.7, 164.9.

(14) (a) Bao, J. M.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S. M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392–3405. (b) VANOL and VAPOL are also commercially available from Aldrich Chemical Co., Inc. and Strem Chemicals.

To a 25 mL flame-dried homemade Schlenk flask (see Supporting Information) equipped with a stir bar and flushed with argon was added (*S*)-VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (116 mg, 0.4 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valuve to dissolve the two reagents, and this was followed by the addition of water (1.8 μL, 0.1 mmol). The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath) for 1 h. After 1 h, a vacuum (0.5 mmHg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 °C (oil bath). The flask was then allowed to cool to room temperature and opened to argon through side arm of the Schlenk flask.

The toluene solution of imine **26h** (354 mg, 1 mmol, prepared as described above) was then directly transferred from the reaction flask in which it was prepared to the flask containing the catalyst utilizing a filter syringe (Corning syringe filters, Aldrich) to remove the 4 Å molecular sieves. The flask that had contained imine **26h** was then rinsed with toluene (0.5 mL), and the rinse was transferred to the flask containing the catalyst under argon flow through side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light yellow solution. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 1 h to afford the crude aziridine as a pale yellow semisolid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27h** as a semisolid in 64% isolated yield (281 mg, 0.64 mmol); *cis*:*trans* not determined. Enamine side products: 15.3% yield of **28h** and 8.3% yield of **29h**. The optical purity of **27h** was determined to be 93% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 4.73 min (major enantiomer, **27h**) and t_R = 5.68 min (minor enantiomer, *ent*-**27h**). The AZ reaction of imine **26h** with (*S*)-VAPOL at 0 °C gave **27h** in 72% yield with 97% ee. With (*R*)-VANOL, *ent*-**27h** was obtained in 73% yield with 94% ee (at room temperature) and 75% yield and 95% ee (at 0 °C). For the reaction at 0 °C, the catalyst was precooled to 0 °C followed by the addition of the imine solution and EDA at 0 °C. Spectral data for **27h**: R_f = 0.28 (4:2:0.1 hexanes/CH_2Cl_2/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72 (t, 3H, J = 7.6 Hz), 0.98−1.08 (m, 1H), 1.11−1.20 (m, 1H), 1.23 (t, 3H, J = 7.1 Hz), 1.38−1.45 (m, 1H), 1.49−1.55 (m, 1H), 1.95 (q, 1H, J = 6.6 Hz), 2.18 (d, 1H, J = 6.8 Hz) 2.22 (s, 12H), 3.39 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.12−4.23 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6, 14.3, 16.1, 16.2, 20.3, 29.9, 43.5, 46.8, 59.6, 59.6, 60.6, 77.3, 127.4, 128.1, 130.4, 130.47, 137.8, 138.2, 155.8, 156.1, 169.7; IR (thin film) 2957vs, 1744s, 1483s, 1221s, 1182vs cm^{-1}; HRMS (ESI-TOF) m/z 440.2817 [(M + H$^+$) calcd for $C_{27}H_{38}NO_4$ 440.2801]; $[\alpha]^{23}_D$ +95.3 (c 1.0, EtOAc) on 97% ee material (HPLC).

The MEDAM aziridines **27b**−**h** were also prepared according to Method B utilizing 5−10 mol % catalyst loading. These results including the yields and optical purity for all of MEDAM aziridines **27** are given in Table 4.

(2*R*,3*R*)-Ethyl-1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl)-3-propylaziridine-2-carboxylate 9h. The imine **8h** was an oil and was generated in situ. To a 10 mL flame-dried round-bottom flask filled with argon were added bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine **10** (468 mg, 1 mmol), 4 Å MS (250 mg, freshly dried), and dry toluene (1.5 mL). After stirring for 10 min, butanal **4h** (78 mg, 1.05 mmol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 4 h. The resulting imine **8h** was used without further purification. Spectral data for **8h**: ^{1}H NMR ($CDCl_3$ 500 MHz) δ 0.98 (t, 3H, J = 7.3 Hz), 1.35 (s, 36H), 1.63 (sextet, 2H, J = 7.3 Hz), 2.31−2.35 (m, 2H), 3.64 (s, 6H), 5.22 (s, 1H), 7.05 (s, 4H), 7.87 (t, 1H, J = 4.9 Hz).

To a 25 mL flame-dried homemade Schlenk flask (see Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (116 mg, 0.4 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents, and this was followed by the addition of water (1.8 μL, 0.1 mmol). The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath for 1 h. After 1 h, a vacuum (0.5 mmHg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 °C (oil bath). The flask was then allowed to cool to 0 °C and opened to argon through side arm of the Schlenk flask.

The toluene solution of imine **8h** (522 mg, 1 mmol, prepared as described above) was then directly transferred from the reaction flask in which it was prepared to the flask containing the catalyst utilizing a filter syringe (Corning syringe filters, Aldrich) to remove the 4 Å molecular sieves. The flask that had contained imine **8h** was then rinsed with toluene (0.5 mL), and the rinse was transferred to the flask containing the catalyst under argon flow through the side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light yellow solution. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL) at 0 °C. The reaction mixture was then warmed to room temperature and transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 1 h to afford the crude aziridine as a pale yellow semisolid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **9h** as a semisolid in 69% isolated yield (419 mg, 0.69 mmol); *cis*:*trans* not determined. Enamine side products: 10.3% yield of **35** and 4.4% yield of **36**. The optical purity of **9h** was determined to be 95% ee by HPLC analysis (Pirkle covalent (R,R) Whelk-O 1 column, 99.5:0.5 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 7.46 min (major enantiomer **9h**) and t_R = 6.60 min (minor enantiomer, *ent*-**9h**). The reaction of imine **9h** with (*R*)-VANOL gave *ent*-**9h** in 75% yield with 93% ee. Spectral data for **9h**: R_f = 0.23 (2:1 hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, 3H, J = 7.5 Hz), 1.31 (t, 3H, J = 7.1 Hz), 1.50−1.74 (m, 2H), 1.45 (s, 18 h), 1.46 (s, 18 h) 1.55−1.73 (m, 2H), 2.15 (q, 1H, J = 6.6 Hz), 2.36 (d, 1H, J = 6.6 Hz), 3.68 (s, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 4.12−4.29 (m, 2H), 7.22 (s, 2H), 7.36 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 14.4, 20.6, 29.9, 32.1, 32.2, 35.8, 35.8, 43.4, 47.3, 60.7, 64.1, 64.1, 77.6, 125.6, 126.2, 136.4, 137.0, 142.9, 142.9, 158.3, 158.7, 170.0; IR (thin film) 2961vs, 1747s, 1448s, 1221s, 1182 vs cm^{-1}; HRMS (ESI-TOF) m/z 608.4665 [(M + H$^+$) calcd for $C_{39}H_{62}NO_4$ 608.4679]; $[\alpha]^{23}_D$ −61.6 (c 1.0, EtOAc) on 93% ee material (HPLC) of *ent*-**9h**.

General Procedure for the Synthesis of MEDAM Aziridines 27 via Method B (without water), Illustrated for Aziridines 27b and 27k. (2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(*o*-tolyl)aziridine-2-carboxylate 27b. Imine **26b** (401.5 mg, 1 mmol) was reacted according to the general Method B described above with (*S*)-VAPOL as ligand with the following differences: (a) water was excluded during the preparation of the catalyst and (b) 3 mol % catalyst loading was utilized. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27b** as a white solid (mp 59−60 °C on 98% ee material) in 91% isolated yield (444 mg, 0.91 mmol); *cis*:*trans* 33:1. Enamine side products: 4.5% yield of **28b** and 2.7% yield of **29b**. The optical purity of **27b** was determined to be 98% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.45 min (major enantiomer, **27b**) and t_R = 12.21 min (minor enantiomer, *ent*-**27b**). The AZ reaction of imine **26b** with (*R*)-VANOL (via Method B and 5 mol % catalyst loading) gave *ent*-**27b** in 90% yield with 97% ee and *cis*:*trans* of 50:1. Spectral data for **27b**: R_f = 0.38 (1:9 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 3H, J = 7.1 Hz), 2.20 (s, 6H), 2.24 (s, 6H), 2.26 (s, 3H), 2.61 (d, 1H, J = 6.8 Hz), 3.08 (d, 1H, J = 6.6 Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.88 (q, 2H, J = 7.1 Hz), 7.01 (d, 1H, J = 6.6 Hz), 7.06−7.09 (m, 2H), 7.13 (s, 2H), 7.18 (s, 2H), 7.53 (d, 1H, J = 6.3 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 13.9, 16.2, 16.2, 18.8, 45.6, 47.2, 59.5, 59.6, 60.4, 77.3, 125.3, 127.1, 127.3, 128.0, 128.6, 129.1, 130.6, 130.6, 133.45, 136.0, 137.9, 138.0, 155.9, 156.2, 168.7; IR (thin film) 2937vs, 1749s, 1485s, 1221s, 1192vs cm^{-1}; HRMS (ESI-TOF) m/z 488.2801 [(M + H$^+$) calcd for $C_{31}H_{38}NO_4$ 488.2801] $[\alpha]^{23}_D$ +46.4 (*c* 1.0, EtOAc) on 97% ee material (HPLC).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-hexylaziridine-2-carboxylate 27k. The imine **26k** was an oil and was generated in situ. To a 10 mL flame-dried round-bottom flask filled with argon were added bis(4-methoxy-3,5-dimethylphenyl)methanamine **25b** (299 mg, 1 mmol), $MgSO_4$ (200 mg, 1.7 mmol, freshly flame-dried), and dry CH_2Cl_2 (3 mL). After stirring for 10 min, heptanal **4k** (120 mg, 1.05 mmol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through Celite, the Celite bed was washed with CH_2Cl_2 (1 mL × 3), and then the filtrate was concentrated by rotary evaporation to give the crude imine as a pale yellow viscous oil which was dried under high vacuum (∼ 0.2 mmHg) for 1 h to remove any excess aldehyde, 100% crude yield. The resulting imine **26k** was used without further purification. Spectral data for **26k**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J = 6.7 Hz), 1.25−1.33 (m, 6H) 1.50−1.55 (m, 2H), 2.22 (s, 12H), 2.28−2.34 (m, 2H), 3.66 (s, 6H), 5.08 (s, 1H), 6.91 (s, 4H), 7.74 (t, 1H, J = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 16.1, 22.6, 26.0, 29.0, 31.6, 35.9, 59.6, 77.7, 127.7, 130.53, 139.2, 155.7, 165.0.

To a 25 mL flame-dried homemade Schlenk flask (see Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VAPOL (16 mg, 0.03 mmol) and $B(OPh)_3$ (35 mg, 0.12 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents. The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath for 1 h. After 1 h, a vacuum (0.5 mmHg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 °C (oil bath). The flask was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask.

Meanwhile, to the flask containing imine **26k** (396 mg, 1 mmol, prepared as described above) was added dry toluene (1.5 mL), and the resultant toluene solution of imine **26k** was then directly transferred from the reaction flask in which it was prepared to the flask containing the catalyst. The flask that had contained imine **26k** was then rinsed with toluene (0.5 mL), and the rinse was transferred to the flask containing the catalyst under argon flow through the side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light yellow solution. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 1 h to afford the crude aziridine as a pale yellow semisolid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2 /EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27k** as a semisolid in 67% isolated yield (323 mg, 0.67 mmol); *cis*:*trans* not determined. Enamine side products: not determined. The optical purity of **27k** was determined to be 90% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.27 min (major enantiomer, **27k**) and t_R = 11.17 min (minor enantiomer, *ent*-**27k**). Spectral data for **27k**: R_f = 0.30 (4:2 hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, J = 7.2 Hz), 0.99−1.03 (m, 1H), 1.14−1.24 (m, 7H), 1.27 (t, 3H, J = 7.1 Hz), 1.48−1.56 (m, 2H), 1.97−2.00 (m, 1H), 2.23 (d, 1H, J = 6.8 Hz), 2.26 (s, 12H), 3.43 (s, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.16−4.25 (m, 2H), 7.04 (s, 2H), 7.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 14.2, 16.0, 16.1, 22.3, 27.1, 27.8, 28.7, 31.7, 43.5, 46.9, 59.4, 60.5, 77.2, 127.3, 128.0, 130.3, 130.4, 137.7, 138.1, 155.7, 156.0, 169.6 (one *sp3* carbon not located); IR (thin film) 2928vs, 1746s, 1483s, 1221s, 1181s cm^{-1}; mass spectrum m/z (% rel intensity) 481 M+ (0.5), 283 (100), 268 (13), 253 (7), 142 (7), 55 (13), 41 (16); $[\alpha]^{23}_D$ +78.3 (*c* 1.0, CH_2Cl_2) on 90% ee material (HPLC).

MEDAM aziridines **27d**, **27e**, **27i**, and **27j** were also prepared according to the Method B (without water) utilizing 2−3 mol % catalyst loading and the results are presented in Table 4.

General Procedure for the Synthesis of MEDAM Aziridines 27 via Method C, Illustrated for Aziridines 27a−27f and 27i−27k. (2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 27a. To a 25 mL flame-dried homemade Schlenk flask (see Figure 1 in the Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VAPOL (16 mg, 0.03 mmol), $B(OPh)_3$ (35 mg, 0.12 mmol), and aldimine **26a** (387 mg, 1 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the reagents. The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 15 min at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow toward the completion of the reaction. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 1 h to afford the crude aziridine as an off-white solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27a** as a white solid

(mp 107−108 °C on 99.8% ee material) in 93% isolated yield (440 mg, 0.93 mmol); *cis*:*trans* > 50:1. Enamine side products: 2.5% yield of **28a** and 2.0% yield of **29a.** The optical purity of **27a** was determined to be 98.5% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.26 min (major enantiomer, **27a**) and t_R = 12.52 min (minor enantiomer, *ent*-**27a**). Spectral data for **27a** given above in procedure for Method B.

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(*o*-tolyl)aziridine-2-carboxylate 27b. Imine **26b** (401.5 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27b** as a white solid (mp 59−60 °C on 98% ee material) in 87% isolated yield (424 mg, 0.87 mmol); *cis*:*trans* 33:1. Enamine side products: 5.0% yield of **28b** and 3.2% yield of **29b**. The optical purity of **27b** was determined to be 96% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.45 min (major enantiomer, **27b**) and t_R = 12.21 min (minor enantiomer, *ent*-**27b**). Spectral data for **27b** given above in procedure for Method B (without H_2O).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(*p*-tolyl)aziridine-2-carboxylate 27c. Imine **26c** (401.5 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27c** as a white solid (mp 116−117 °C on 99.5% ee material) in 94% isolated yield (458 mg, 0.94 mmol); *cis*:*trans* > 50:1. Enamine side products: 3.0% yield of **28c** and 1.2% yield of **29c**. The optical purity of **27c** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.22 min (major enantiomer, **27c**) and t_R = 11.62 min (minor enantiomer, *ent*-**27c**). Spectral data for **27c**: R_f = 0.30 (1:9 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (t, 3H, J = 7.1 Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.26 (s, 3H), 2.52 (d, 1H, J = 6.6 Hz), 3.07 (d, 1H, J = 6.8 Hz), 3.62 (s, 3H), 3.64 (s, 1H), 3.68 (s, 3H) 3.93 (dq, 2H, J = 3.2 Hz, 7.1 Hz), 7.02 (d, 2H, J = 7.8 Hz), 7.08 (s, 2H), 7.17 (s, 2H), 7.24 (d, 2H, J = 8.0 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.1, 16.2, 16.2, 21.1, 46.2, 48.2, 59.5, 59.6, 60.4, 77.1, 127.4, 127.7, 127.8, 128.4, 130.5, 130.6, 132.3, 136.8, 137.9, 138.0, 155.9, 156.1, 168.1; IR (thin film) 2978vs, 1748s, 1483s, 1221s, 1190vs cm^{-1}; HRMS (ESI-TOF) m/z 488.2806 [(M + H$^+$) calcd for $C_{31}H_{38}NO_4$ 488.2801]; $[\alpha]^{23}_D$ +29.4 (*c* 1.0, EtOAc) on 99.8% ee material (HPLC).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-methoxyphenyl)aziridine-2-carboxylate 27d. Imine **26d** (417.5 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27d** as a white solid (mp 56−57 °C on 98% ee material) in 83% isolated yield (418 mg, 0.83 mmol); *cis*:*trans* > 50:1. Enamine side products: 1.2% yield of **28d** and 2.1% yield of **29d**. The optical purity of **27d** was determined to be 97% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 12.07 min (major enantiomer, **27d**) and t_R = 19.20 min (minor enantiomer, *ent*-**27d**). Spectral data for **27d**: R_f = 0.28 (1:9 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, J = 7.1 Hz), 2.19 (s, 6H), 2.24 (s, 6H), 2.51 (d, 1H, J = 6.8 Hz), 3.06 (d, 1H, J = 6.8 Hz), 3.63 (s, 3H), 3.65 (s, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 3.89−3.99 (m, 2H), 6.77 (d, 2H, J = 9.5 Hz), 7.09 (s, 2H), 7.18 (s, 2H), 7.29 (d, 2H, J = 8.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.1, 16.2, 16.2, 46.2, 47.9, 55.2, 59.5, 59.6, 60.5, 77.1, 113.2, 127.4, 127.8, 128.9, 130.6, 130.6, 137.8, 138.0, 155.9, 156.1, 158.9, 168.1 (one sp^2 carbon not located); IR (thin film) 2942vs, 1743s, 1514s, 1250s, 1180vs cm^{-1}; HRMS (ESI-TOF) m/z 504.2744 [(M + H$^+$) calcd for $C_{31}H_{38}NO_5$ 504.2750] $[\alpha]^{23}_D$ −25 (*c* 1.0, EtOAc) on 96% ee material (HPLC) on *ent*-**27d**.

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-bromophenyl)aziridine-2-carboxylate 27e. Imine **26e** (466.4 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 5:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27e** as a white solid (mp 145−146 °C on 99.6% ee material) in 94% isolated yield (519 mg, 0.94 mmol); *cis*:*trans* > 50:1. Enamine side products: 1.5% yield of **28e** and 1.9% yield of **29e**. The optical purity of **27e** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 8.41 min (major enantiomer, **27e**) and t_R = 11.96 min (minor enantiomer, *ent*-**27e**). Spectral data for **27e**: R_f = 0.32 (1:9 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, J = 7.1 Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.56 (d, 1H, J = 6.6 Hz), 3.03 (d, 1H, J = 6.8 Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.89−3.98 (m, 2H), 7.06 (s, 2H), 7.16 (s, 2H), 7.26 (d, 2H, J = 8.5 Hz), 7.35 (d, 2H, J = 8.5 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.1, 16.2, 16.2, 46.4, 47.5, 59.6, 59.6, 60.6, 121.2, 127.4, 127.7, 129.6, 130.7, 130.8, 134.4, 137.6, 137.8, 156.0, 156.2, 167.7 (one sp^2 and one sp^3 carbon not located); IR (thin film) 2942vs, 1745vs, 1485vs, 1221vs cm^{-1}; HRMS (ESI-TOF) m/z 552.1733 [(M + H$^+$) calcd for $C_{30}H_{35}NO_4{}^{79}Br$ 552.1749] $[\alpha]^{23}_D$ +12.8 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-nitrophenyl)aziridine-2-carboxylate 27f. Imine **26f** (432.5 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 5:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27f** as a white solid (mp 174−175 °C on 99.7% ee material) in 95% isolated yield (493 mg, 0.95 mmol); *cis*:*trans* > 50:1. Enamine side products: 1.2% yield of **28f** and 2.0% yield of **29f**. The optical purity of **27f** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 17.12 min (major enantiomer, **27f**) and t_R = 27.13 min (minor enantiomer, *ent*-**27f**). Spectral data for **27f**: R_f = 0.30 (1:9 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, J = 7.1 Hz), 2.18 (s, 6H), 2.25 (s, 6H), 2.68 (d, 1H, J = 6.8 Hz), 3.15 (d, 1H, J = 6.8 Hz), 3.62 (s, 3H), 3.68 (s, 3H), 3.71 (s, 1H), 3.93 (dq, 2H, J = 2.2, 7.1 Hz), 7.06 (s, 2H), 7.16 (s, 2H), 7.57 (d, 2H, J = 8.8 Hz), 8.10 (d, 2H, J = 8.8 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.1, 16.2, 16.2, 46.8, 47.3, 59.6, 59.6, 60.9, 76.9, 123.0, 127.3, 127.6, 128.8, 130.8, 130.9, 137.3, 137.5, 142.8, 147.3, 156.1, 156.3, 167.2; IR (thin film) 2984 vs, 1745 vs, 1603 s, 1522 vs, 1221 vs cm^{-1}; HRMS (ESI-TOF) m/z 519.2505 [(M + H$^+$) calcd for $C_{30}H_{35}N_2O_6$ 519.2495] $[\alpha]^{23}_D$ −4.8 (*c* 1.0, EtOAc) on 99.8% ee material (HPLC).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridine-2-carboxylate 27i. Imine **26i** (393.5 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 2:1 hexanes/CH_2Cl_2 as eluent, gravity column) afforded pure cis-aziridine **27i** as a white solid (mp 47−49 °C on 91% ee material) in 96% isolated yield (461 mg, 0.96 mmol); *cis*:*trans* 50:1. Enamine side products: not determined. The optical purity of **27i** was determined to be 89% ee by HPLC analysis (CHIRALCEL OD column, 99:1 hexane/2-propanol at 223 nm, flow rate 0.7 mL/min): retention times t_R = 10.06 min (major enantiomer, **27i**) and t_R = 12.37 min (minor enantiomer, *ent*-**27i**). Spectral data for **27i**: R_f = 0.21 (2:1 hexane/CH_2Cl_2); ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 0.46−0.57 (m, 1H), 0.87−1.19 (m, 4H), 1.21 (t, 3H, J = 7.1 Hz), 1.22−1.32 (m, 2H), 1.40−1.60 (m, 4H), 1.71−1.76 (m, 1H), 2.16 (m, 1H), 2.19 (s, 6H), 2.20 (s, 6H), 3.35 (s, 1H), 3.60 (s, 3H), 3.63 (s, 3H), 4.10−4.25 (m, 2H), 6.95 (s, 2H), 7.10 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 15.6, 15.7, 24.9, 25.1, 25.7, 29.7, 30.9, 35.9, 43.0, 51.8, 59.0, 59.1, 60.1, 77.0, 126.9, 128.1, 129.8, 130.0, 137.2, 137.7, 155.3, 155.8, 169.3; IR (thin film) 2928vs, 1744s, 1483s, 1221s, 1181s, 1017 m cm^{-1}; mass spectrum m/z (% rel intensity) 479 M+ (0.7), 283 (100), 268 (25), 253 (12), 237 (7), 210 (7), 195 (9), 141 (8), 95 (10), 67 (16), 55 (10), 41 (16); $[\alpha]^{23}_D$ +107.4 (c 1.0, CH_2Cl_2) on 89% ee material (HPLC).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-*tert*-butylaziridine-2-carboxylate 27j. Imine **26j** (367.5 mg, 1 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2/ether as eluent, gravity column) afforded pure *cis*-aziridine **27j** as a semisolid in 93% isolated yield (422 mg, 0.93 mmol); *cis*:*trans* 50:1. Enamine side products: not determined. The optical purity of **27j** was determined to be 92% ee by HPLC analysis (CHIRALCEL OD column, 99:1 hexane/2-propanol at 226 nm, flow rate 1.0 mL/min): retention times t_R = 6.8 min (major enantiomer, **27j**) and t_R = 10.55 min (minor enantiomer, *ent*-**27j**). Spectral data for **27j**: R_f = 0.28 (1:2 hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 (s, 9H), 1.29 (t, 3H, J = 7.1 Hz), 1.70 (d, 1H, J = 7.3 Hz), 2.11 (d, 1H, J = 7.2 Hz), 2.24 (s, 6H), 2.26 (s, 6H), 3.38 (s, 1H), 3.63 (s, 3H), 3.66 (s, 3H), 4.05−4.26 (m, 2H), 7.04 (s, 2H), 7.30 (s, 2H); 13C NMR ($CDCl_3$, 75 MHz) δ 13.9, 15.8, 16.0, 27.2, 31.4, 43.2, 55.9, 59.2, 59.3, 60.2, 78.2, 127.3, 128.2, 130.0, 137.8, 138.7, 155.5, 156.0, 169.7 (one *sp2* carbon not located); IR (thin film) 2953vs, 1747s, 1481s, 1221s, 1181s, 1017 m cm^{-1}; mass spectrum m/z (% rel intensity) 453 M+ (1), 283 (100), 268 (45), 253 (26), 237 (17), 225 (11), 210 (13), 195 (17), 164 (9) 141 (26), 132 (11), 127 (12), 91 (11), 69 (18), 55 (37), 41 (55); $[\alpha]^{23}_D$ +110.0 (c 1.0, CH_2Cl_2) on 94% ee material (HPLC).

(2*R*,3*R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-hexylaziridine-2-carboxylate 27k. To a 25 mL flame-dried homemade Schlenk flask (see Figure 1 in the Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VANOL (16 mg, 0.3 mmol) and $B(OPh)_3$ (35 mg, 0.12 mmol). Meanwhile, to the flask containing imine **26k** (396 mg, 1 mmol, prepared as described above) was added dry toluene (1.5 mL), and the resultant toluene solution of imine **26k** was then directly transferred from the reaction flask in which it was prepared to the flask containing the ligand and $B(OPh)_3$. The flask that had contained imine **26k** was then rinsed with toluene (0.5 mL), and the rinse was transferred to the flask containing the ligand and $B(OPh)_3$ under argon flow through the side arm of the Schlenk flask. The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was rapidly added ethyl diazoacetate (EDA) **2** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 5 min to afford the crude aziridine as a pale yellow semisolid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2 /EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **27k** as a semisolid in 64% isolated yield (308 mg, 0.64 mmol); *cis*:*trans* not determined. Enamine side products: 10% yield of **28k** and 0% yield of **29k**. The optical purity of **27k** was determined to be 86% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226 nm, flow rate 0.7 mL/min): retention times t_R = 9.27 min (major enantiomer, **27k**) and t_R = 11.17 min (minor enantiomer, *ent*-**27k**). Spectral data for **27k** is given above under the procedure for Method B (without H_2O).

General Procedure for the deprotection of *N*-MEDAM aziridines 27 to give N−H aziridines 12. (2*R*,3*R*)-Ethyl 3-phenylaziridine-2-carboxylate 12a. To a 25 mL flame-dried round-bottom flask filled with argon were added aziridine **27a** (237 mg, 0.5 mmol, 99% ee) and anisole (5.4 mL, freshly distilled) at room temperature. The flask was cooled to 0 °C, and triflic acid (200 μL, 2.5 mmol) was added. The ice-bath was removed, and the reaction mixture was stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous Na_2CO_3 solution until the pH was greater than 9. After addition of ether (3 mL) and water (1 mL), the organic layer was separated, and the water layer was extracted with ether (5 mL × 3). The combined organic layer was washed with saturated aqueous NaCl solution (10 mL × 3) and dried over anhydrous $MgSO_4$. The ether was removed by rotary evaporation, and most of the anisole was removed by high vacuum for a short period of time (∼15 min) leaving an off-white sticky residue. Exposure to high vacuum for extended periods results in loss of **12a** to sublimation. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether/hexanes as eluent) afforded **12a** as a white solid (mp 58−59 °C) in 95% isolated yield (91 mg, 0.475 mmol). The optical purity of **12a** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-propanol at 228 nm, flow rate 1.0 mL/min): retention times t_R = 3.99 min (major enantiomer, **12a**) and t_R = 3.47 min (minor enantiomer, *ent*-**12a**). Spectral data for **12a**: R_f = 0.13 (1:1 Et_2O/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, J = 7.1 Hz), 1.87 (br, s, 1H), 3.00 (d, 1H, J = 6.1 Hz), 3.47 (d, 1H, J = 6.1 Hz), 3.90−4.00 (m, 2H), 7.24−7.33 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.9, 29.7, 37.1, 61.1, 127.5, 127.6, 128.0, 134.8, 169.0; $[\alpha]^{23}_D$ −12.4 (c 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[3f]

(2*R*,3*R*)-Ethyl 3-(*o*-tolyl)aziridine-2-carboxylate 12b. Aziridine **27b** (244 mg, 0.5 mmol, 99% ee) was reacted according to the general method described above except that the reaction time was 1 h. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether/hexanes as eluent) afforded **12b** as a white solid (mp 84.5−85.5 °C) in 97% isolated yield (100 mg, 0.485 mmol). The optical purity of **12b** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 228 nm, flow rate 0.7 mL/min): retention times t_R = 6.4 min (major enantiomer, **12b**) and t_R = 5.5 min (minor enantiomer, *ent*-**12b**). Spectral data for **12b**: R_f =0.11 (1:1 Et_2O/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, J = 7.1 Hz), 1.72 (br, s, 1H), 2.32 (s, 3H), 3.04 (d, 1H, J = 6.1 Hz), 3.35 (d, 1H, J = 6.1 Hz), 3.92 (q, 2H, J = 7.1 Hz), 7.09−7.17 (m, 3H), 7.23−7.24 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.9, 18.8, 29.7, 36.5, 61.1, 125.5, 127.2, 127.6, 129.5, 133.3, 136.9, 169.3; $[\alpha]^{23}_D$ −96.9 (c 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[3f]

(2*R*,3*R*)-Ethyl 3-(4-bromophenyl)aziridine-2-carboxylate 12e. Aziridine **27e** (276 mg, 0.5 mmol, 99.5% ee) was reacted according to the general method described above except that the reaction time was 1 h. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether/hexanes as eluent) afforded **12e** as a white solid (mp 78.5−79 °C) in 96% isolated yield (130 mg, 0.48 mmol). The optical purity of **12e** was determined to be 99.5% ee by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 228 nm, flow rate 0.7 mL/min): retention times t_R = 8.24 min (major enantiomer, **12e**) and t_R = 7.07 min

(minor enantiomer, *ent*-**12e**). Spectral data for **12e**: R_f = 0.12 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, 3H, J = 7.1 Hz), 1.67 (br, s, 1H), 3.01 (d, 1H, J = 6.6 Hz), 3.40 (d, 1H, J = 6.4 Hz), 3.93−3.98 (m, 2H), 7.20 (d, 2H, J = 8.5 Hz), 7.41 (d, 2H, J = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.9, 37.1, 39.0, 61.1, 121.5, 129.2, 131.0, 133.9, 168.6; $[\alpha]^{23}_D$ +11.92 (*c* 1.0, EtOAc) on 99.5% ee material (HPLC). These spectral data match those previously reported for this compound.[3f]

(2*R*,3*R*)-Ethyl 3-(4-nitrophenyl)aziridine-2-carboxylate 12f. Aziridine **27f** (259 mg, 0.5 mmol, 97% ee) was reacted according to the general method described above except that the reaction time was 1 h. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether/hexanes as eluent) afforded **12f** as a white solid (mp 89−90.5 °C) in 97% isolated yield (115 mg, 0.485 mmol). The optical purity of **12f** was determined to be 97% ee by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 228 nm, flow rate 0.7 mL/min): retention times t_R = 13.75 min (major enantiomer, **12f**) and t_R = 11.92 min (minor enantiomer, *ent*-**12f**). Spectral data for **12f**: R_f = 0.07 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, 3H, J = 7.1 Hz), 1.80 (br, s, 1H), 3.13 (d, 1H, J = 6.3 Hz), 3.56 (d, 1H, J = 6.6 Hz), 3.92−3.97 (m, 2H), 7.54 (d, 2H, J = 8.3 Hz), 8.15 (d, 2H, J = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.8, 37.4, 61.1, 122.9, 128.6, 142.6, 147.1, 168.1; $[\alpha]^{23}_D$ −15.6 (*c* 1.0, EtOAc) on 97% ee material (HPLC). These spectral data match those previously reported for this compound.[3f]

(2*R*,3*R*)-Ethyl 3-propylaziridine-2-carboxylate 12h. Aziridine **27h** (220 mg, 0.5 mmol, 93% ee) was reacted according to the general method described above except that the reaction time was 1 h, the reaction temperature was 65 °C, and an air condenser was utilized. Purification by silica gel chromatography (18 mm × 230 mm, 1:3 ether/pentane as eluent) afforded **12h** as a light yellow liquid in 72% isolated yield (57 mg, 0.36 mmol). The optical purity of **12h** was determined to be 93% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-propanol at 222 nm, flow rate 0.7 mL/min): retention times t_R = 5.06 min (major enantiomer, **12h**) and t_R = 5.88 min (minor enantiomer, *ent*-**12h**). The yield of **12h** was determined to be 76% by ^1H NMR analysis of the crude reaction mixture with Ph_3CH as internal standard. Spectral data for **12h**: R_f = 0.13 (1:1 Et_2O/hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz), 1.22−1.40 (m, 3H), 1.40−1.50 (m, 2H), 2.04−2.10 (m, 1H), 2.49 (d, 1H, J = 6.0 Hz), 4.08 (q, 2H, J = 7.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.5, 14.0, 20.7, 29.6, 34.3, 38.3, 61.0, 170.7. These spectral data match those previously reported for this compound.[3f]

(2*R*,3*R*)-Ethyl 3-(cyclohexyl)aziridine-2-carboxylate 12i. Aziridine **27i** (240 mg, 0.5 mmol, 99% ee) was reacted according to the general method described above except that the reaction time was 0.5 h, the reaction temperature was 65 °C, and an air condenser was utilized. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether/hexanes as eluent) afforded **12i** as a white solid (mp 58−59 °C) in 90% isolated yield (89 mg, 0.45 mmol). The optical purity of **12i** was determined to be 99% ee by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-propanol at 228 nm, flow rate 1.0 mL/min): retention times t_R = 3.99 min (major enantiomer, **12i**) and t_R = 3.47 min (minor enantiomer, *ent*-**12i**).−Spectral data for **12i**: R_f = 0.19 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (br, s, 1H), 1.09−1.20 (m, 6H), 1.24 (t, 3H, J = 7.1 Hz), 1.43−1.46 (m, 1H), 1.61−1.70 (m, 3H), 1.86−1.92 (m, 2H), 2.60 (d, 1H, J = 6.1 Hz), 4.18 (q, 2H, J = 7.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.1, 25.4, 25.4, 26.0, 30.8, 31.6, 34.2, 36.9, 44.0, 61.1, 171.0; $[\alpha]^{23}_D$ −62.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[3f]

(2*R*,3*R*)-Ethyl 3-(*tert*-butyl)aziridine-2-carboxylate 12j. Aziridine **27j** (227 mg, 0.5 mmol, 99% ee) was reacted according to the general method described above except that the reaction time was 0.5 h, the reaction temperature was 65 °C, and an air condenser was utilized. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether/hexanes as eluent) afforded **12j** as a colorless oil in 88% isolated yield (75 mg, 0.44 mmol). The optical purity of **12j** was determined to be 97% ee by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 228 nm, flow rate 1.0 mL/min): retention times t_R = 9.95 min (major enantiomer, **12**) and t_R = 8.38 min (minor enantiomer, *ent*-**12j**). Spectral data for **12j**: R_f = 0.10 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 9H), 1.23 (t, 3H, J = 6.9 Hz), 1.48 (br, s, 1H), 2.09 (d, 1H, J = 6.1 Hz), 2.61 (d, 1H, J = 6.6 Hz), 4.04−4.23 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.0, 27.4, 31.5, 35.3, 47.4, 61.0, 170.2; $[\alpha]^{23}_D$ −23.7 (*c* 1.0, EtOAc) on 97% ee material (HPLC). These spectral data match those previously reported for this compound.[3f]

General Procedure for the Aziridination of Diazoacetamides, Illustrated for Aziridines 31a, 32a, 33a, and 34a. (2*R*,3*R*)-1-Benzhydryl-*N*-benzyl-*N*-methyl-3-phenylaziridine-2-carboxamide 31a. To a 25 mL flame-dried homemade Schlenk flask (see Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (87 mg, 0.3 mmol). Under an argon flow through the side arm of the Schlenk flask, dry CCl_4 (2 mL) was added through the top of the Teflon valve to dissolve the two reagents. The flask was sealed by closing the Teflon valve and then placed in an 85 °C oil bath for 1 h. After 1 h, a vacuum (0.5 mmHg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 85 °C (oil bath). The flask was then allowed to cool to room temperature and opened to argon through side arm of the Schlenk flask.

To the flask containing the catalyst were first added the aldimine **1a** (271 mg, 1 mmol) and then dry CCl_4 (2 mL) under an argon flow through side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light orange solution. To this solution was rapidly added diazoacetamide **30** (200 mg, 1.05 mmol) (see Supporting Information) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2), and the rinse was added to the 100 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mmHg) for 5 min to afford the crude aziridine as an off-white solid. Purification of the crude aziridine by silica gel chromatography (25 mm × 550 mm column, 5:1 hexanes/EtOAc as eluent) afforded pure *cis*-aziridine **31a** as a white solid (mp 179−180 °C on 88% ee material) in 14% isolated yield (61 mg, 0.14 mmol). Only the *cis* isomer was observed from ^1H NMR analysis of the crude reaction mixture. Enamine side products: not determined. The optical purity of **31a** was determined to be 88% ee by HPLC analysis (CHIRALCELL OD-H column, 95:5 hexane/2-propanol at 225 nm, flow rate 0.7 mL/min): retention times t_R = 26.44 min (major enantiomer, **31a**) and t_R = 18.30 min (minor enantiomer, *ent*-**31**). Compound **31a** appeared as a mixture of two rotamers in the ^1H NMR spectrum at the room temperature in a 2.5: 1 molar ratio. The ^1H NMR data given below is for the major rotamer and was extracted from the ^1H NMR spectrum of the mixture. Spectral data for **31a**: R_f = 0.15 (1:5 EtOAc/Hexane); ^1H NMR ($CDCl_3$, 300 MHz) (major rotamer) δ 2.72 (s, 3H), 2.81 (d, 1H, J = 6.6 Hz), 3.17 (d, 1H, J = 6.8 Hz), 3.68 (d, 1H, J = 15.1 Hz), 4.01 (s, 1H), 5.02 (d, 1H, J = 14.9 Hz), 6.47 (d, 2H, J = 6.9 Hz), 7.01−7.52 (m, 16H), 7.78 (d, 2H, J = 7.1 Hz); mass spectrum, m/z (% rel intensity) 432 M^+ (0.06), 284 (5), 265 (100), 194 (7), 181 (9), 167 (72), 152 (31), 188 (30), 91 (100), 77 (18), 65 (18), 42(14); $[\alpha]^{23}_D$ +71.2 (*c* 1.0 in CH_2Cl_2) on 88% ee material (HPLC).

(2*R*,3*R*)-*N*-Benzyl-1-(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)-methyl)-*N*-methyl-3-phenylaziridine-2-carboxamide 32a. To a 25 mL flame-dried homemade Schlenk flask (see Supporting Information) equipped with a stir bar and flushed with argon were added (*S*)-VAPOL (27 mg, 0.05 mmol) and $B(OPh)_3$ (58 mg, 0.2 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents, and this was followed by the addition of water (0.9 μL, 0.05 mmol). The flask was sealed by closing the Teflon valve and then placed in an 80 °C oil bath for 1 h. After 1 h, a vacuum (0.5 mmHg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 °C (oil bath). The flask was then allowed to cool to room temperature and opened to argon through side arm of the Schlenk flask.

The rest of the procedure was the same as that followed for aziridine **31a** utilizing imine **8a** (278 mg, 0.5 mmol) and diazoacetamide **30** (100 mg, 0.525 mmol) (see Supporting Information) and toluene (1 mL). Purification of the crude aziridine by silica gel chromatography (25 mm × 400 mm column, 1:20:20 EtOAc/CH_2Cl_2/hexanes as the first eluent to remove a strong UV absorpting fraction, then change to 1:3 Et_2O/hexanes as the second eluent) afforded pure *cis*-aziridine **32a** as a white solid (mp 169−170 °C on 93% ee material) in 40% isolated yield (145 mg, 0.2 mmol). This reaction went to 42% completion in 24 h. Only the *cis* isomer was observed from ^{1}H NMR analysis of the crude reaction mixture. Enamine side products: not determined. The optical purity of **32a** was determined to be 93% ee by HPLC analysis (CHIRALCELL OD-H column, 90:10 hexane/2-propanol at 228 nm, flow rate 0.7 mL/min): retention times t_R = 9.94 min (major enantiomer, **32a**) and t_R = 8.45 min (minor enantiomer, *ent*-**32a**). Compound **32a** appeared as a mixture of two rotamers in the ^{1}H NMR spectrum at the room temperature in a 3: 1 molar ratio. The ^{1}H NMR data given below is for the major rotamer and was extracted from the ^{1}H NMR spectrum of the mixture. Spectral data for **32a**: R_f = 0.65 (1:3 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) (major rotamer) δ 1.34 (s, 18H), 1.47 (s, 18H), 2.80 (s, 3H), 2.87 (d, 1H, J = 6.8 Hz), 3.16 (d, 1H, J = 6.7 Hz), 3.63 (s, 3H), 3.70 (s, 3H), 3.95 (s, 1H), 3.98 (d, 1H, J = 14.9 Hz), 4.82 (d, 1H, J = 14.9 Hz), 6.57 (d, 2H, J = 7.0 Hz), 7.08−7.13 (m, 3H), 7.30−7.33 (m, 3H), 7.41 (s, 2H), 7.54−7.56 (m, 2H), 7.62 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 32.0, 32.2, 33.3, 35.7, 35.8, 47.7, 48.2, 50.2, 63.9, 64.0, 77.6, 125.5, 125.8, 126.7, 126.9, 127.2, 127.4, 127.6, 128.1, 128.2, 136.7, 136.8, 137.1, 142.8, 143.0, 158.0, 158.1, 165.7; IR (thin film) 2961vs, 1663s, 1414s, 1221s cm^{-1}; mass spectrum, m/z (% rel intensity) 716 M^+ (0.36), 451 (26), 265 (29), 120 (14), 118 (13), 91 (100), 58 (84), 42 (24); $[\alpha]^{23}_D$ +14.3 (c 1.0 in CH_2Cl_2) on 97% ee material (HPLC).

(2*R*,3*R*)-*N*-Benzyl-1-(bis(3,5-dimethylphenyl)methyl)-*N*-methyl-3-phenylaziridine-2-carboxamide 33a. Imine **19a** (164 mg, 0.5 mmol) was reacted with diazoacetamide **30** (100 mg, 0.525 mmol) following the procedure used for aziridine **32a** (given above). Purification of the crude aziridine by silica gel chromatography (25 mm × 400 mm column, 1:20:20 EtOAc/CH_2Cl_2/hexanes as the first eluent to remove to remove a strong UV absorpting fraction, then change to 1:3 Et_2O/hexanes as the second eluent) afforded pure *cis*-aziridine **33a** as a white solid (mp 168−169 °C on 97% ee material) in 66% isolated yield (161 mg, 0.33 mmol). Only the *cis* isomer was observed from ^{1}H NMR analysis of the crude reaction mixture. Enamine side products: not determined. The optical purity of **33a** was determined to be 97% ee by HPLC analysis (CHIRALCELL OD-H column, 90:10 hexane/2-propanol at 228 nm, flow rate 0.7 mL/min): retention times t_R = 15.84 min (major enantiomer, **33a**) and t_R = 11.77 min (minor enantiomer, *ent*-**33a**). The compound **33a** appeared as a mixture of two rotamers in the ^{1}H NMR spectrum at the room temperature in a 3: 1 molar ratio. The ^{1}H NMR data given below is for the major rotamer and was extracted from the ^{1}H NMR spectrum of the mixture. Spectral data for **33a**: R_f = 0.45 (1:3 EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) (major rotamer) δ 2.26 (s, 6H), 2.38 (s, 6H), 2.79 (s, 3H), 2.81 (d, 1H, J = 6.8 Hz), 3.17 (d, 1H, J = 6.8 Hz), 3.80 (d, 1H, J = 14.9 Hz), 3.89 (s, 1H), 5.01 (d, 1H, J = 14.9 Hz), 6.54 (d, 2H, J = 7.3 Hz), 6.82 (s, 1H), 6.92 (s, 1H), 7.09−7.15 (m, 2H), 7.22 (s, 2H), 7.31−7.33 (m, 3H), 7.46 (s, 2H), 7.49−7.51 (m, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 21.3, 21.4, 33.2, 47.4, 48.0, 50.2, 78.2, 125.3, 126.7, 127.1, 127.4, 128.0, 128.2, 128.5, 128.6, 128.7, 128.8, 135.7, 136.7, 137.57, 137.7, 142.5, 142.8, 165.7; IR (thin film) 2919s, 1659vs, 1452s, 731s cm^{-1}; mass spectrum, m/z (% rel intensity) 488 M^+ (0.04), 340 (5), 265 (100), 239 (10), 223 (75), 208 (33), 193 (62), 178 (15), 120 (22), 91 (100), 65 (16), 42 (25). Anal. Calcd for $C_{34}H_{36}N_2O$: C, 83.57; H, 7.43; N, 5.73. Found: C, 83.20; H, 7.90; N, 5.52; $[\alpha]^{23}_D$ +58.3 (c 1.0 in CH_2Cl_2) on 97% ee material (HPLC).

(2*R*,3*R*)-*N*-Benzyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-methyl-3-phenylaziridine-2-carboxamide 34a. Imine **26a** (194 mg, 0.5 mmol) was reacted with diazoacetamide **30** (100 mg, 0.525 mmol) following the procedure used for aziridine **32a** (given above) except that 20 mol % catalyst loading was utilized. Purification of the crude aziridine by silica gel chromatography (25 mm × 400 mm column, 1:20:20 EtOAc/CH_2Cl_2/hexanes as the first eluent to remove a strong UV absorpting fraction, then change to 1:2 Et_2O/hexanes as the second eluent) afforded pure *cis*-aziridine **34a** as a white solid (mp 164−165 °C on 98% ee material) in 77% isolated yield (213 mg, 0.39 mmol). Only the *cis* isomer was observed from ^{1}H NMR analysis of the crude reaction mixture. Enamine side products: not determined. The optical purity of **34a** was determined to be 98% ee by HPLC analysis (CHIRALCELL OD-H column, 90:10 hexane/2-propanol at 222 nm, flow rate 1.0 mL/min): retention times t_R = 18.80 min (major enantiomer, **34a**) and t_R = 13.80 min (minor enantiomer, *ent*-**34a**). The same reaction with 10 mol % of (*S*)-VAPOL/$B(OPh)_3$ catalyst went to 68% completion and gave **34a** in 60% yield with 96% ee in 24 h. The compound **34a** appeared as a mixture of two rotamers in the ^{1}H NMR spectrum at the room temperature in a 3: 1 molar ratio. The ^{1}H NMR data given below is for the major rotamer and was extracted from the ^{1}H NMR spectrum of the mixture. Spectral data for **34a**: R_f = 0.28 (1:3 EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) (major rotamer) δ 2.20 (s, 6H), 2.31 (s, 6H), 2.76 (d, 1H, J = 6.8 Hz), 2.77 (s, 3H), 3.12 (d, 1H, J = 6.8 Hz), 3.65 (s, 3H), 3.72 (s, 3H), 3.78 (s, 1H), 3.79 (d, 1H, J = 14.4 Hz), 4.98 (d, 1H, J = 14.9 Hz), 6.51 (d, 2H, J = 7.2 Hz), 7.05−7.12 (m, 3H), 7.18 (s, 2H), 7.26−7.30 (m, 3H), 7.42 (s, 2H), 7.45−7.47 (m, 2H); ^{13}C ($CDCl_3$, 125 MHz) δ 16.2, 16.2, 33.2, 47.4, 48.1, 50.2, 59.5, 59.6, 77.4, 126.7, 127.2, 127.4, 127.7, 127.7, 127.9, 128.0, 128.1, 128.2, 130.4, 130.5, 135.8, 136.7, 137.9, 138.3, 155.9, 165.8; IR (thin film) 2928vs, 1659vs, 1483s, 1221s cm^{-1}; mass spectrum, m/z (% rel intensity) 548 M^+ (0.05), 400 (7), 283 (100), 265 (33), 253 (9), 120 (11), 91 (100), 43 (11); $[\alpha]^{23}_D$ +51.6 (c 1.0 in CH_2Cl_2) on 98% ee material (HPLC).

^{1}H NMR studies in C_6D_6 at 25 and 80 °C. ^{1}H NMR (C_6D_6, 500 MHz, 25 °C) (major rotamer): δ 2.08 (s, 6H), 2.19 (s, 3H), 2.32 (s, 6H), 2.42 (d, 1H, J = 6.7 Hz), 2.82 (d, 1H, J = 6.7 Hz), 3.15 (s, 3H), 3.30 (s, 3H), 3.48 (d, 1H, J = 15.0 Hz), 3.77 (s, 1H), 5.00 (d, 1H, J = 14.9 Hz), 6.42 (d, 2H, J = 7.8 Hz), 6.93−6.95 (m, 4H), 7.05 (t, 2H, J = 7.9 Hz), 7.41 (s, 2H), 7.52 (d, 2H, J = 7.7 Hz), 7.90 (s, 2H). ^{1}H NMR (C_6D_6, 500 MHz, 25 °C) (minor rotamer): δ 2.06 (s, 6H), 2.27 (s, 6H), 2.40 (s, 3H), 2.60 (d, 1H, J = 6.7 Hz), 2.76 (d, 1H, J = 6.6 Hz), 3.14 (s, 3H), 3.25 (s, 3H), 3.68 (s, 1H), 3.86 (d, 1H, J = 16.1 Hz), 4.19 (d, 1H, J = 16.1 Hz), 6.53−6.55 (m, 2H), 6.97−7.00 (m, 4H), 7.10 (t, 2H, J = 7.7 Hz), 7.35 (s, 2H), 7.56 (d, 2H, J = 7.7 Hz), 7.77 (s, 2H). The ^{1}H NMR spectrum at 80 °C indicated the presence of one species: ^{1}H NMR (C_6D_6, 500 MHz, 80 °C): δ 2.07 (s, 6H), 2.26 (s, 6H), 2.33

(s, 3H), 2.52 (s, 1H), 2.85 (d, 1H, J = 6.2 Hz), 3.23 (s, 3H), 3.35 (s, 3H), 3.78 (s, 2H), 4.74 (s, 1H), 6.57 (s, 2H), 6.94−6.99 (m, 1H), 6.97−7.01 (m, 1H), 7.06 (t, 2H, J = 7.2 Hz), 7.13 (s, 2H), 7.32 (s, 2H), 7.48 (d, 2H, J = 7.3 Hz), 7.73 (s, 2H).

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Supporting Information Available: Procedures for the preparation for the DAM imines **15** and the MEDAM imines **26**, for the syntheses of the DAM aziridines **11** and the diazoacetamide **30**, and for the data used in Charts II and III, as well as ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.