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Double Stereodifferentiation in the Catalytic Asymmetric Aziridination of Imines Prepared from α-Chiral Amines

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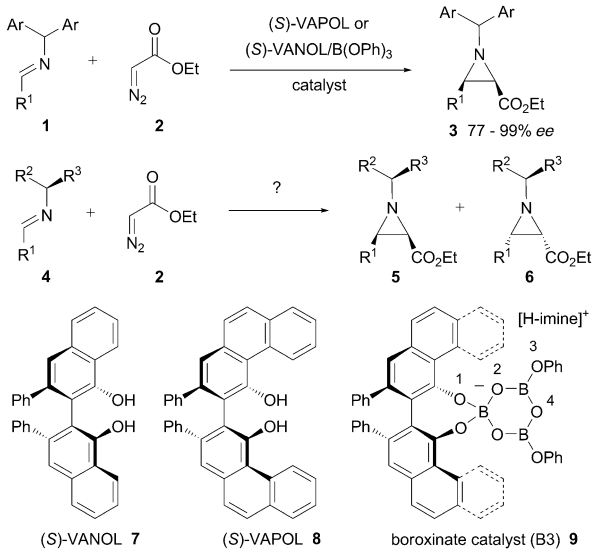
Abstract: The catalytic asymmetric aziridination of imines and diazo compounds (AZ reaction) mediated by boroxinate catalysts derived from the VANOL and VAPOL ligands was investigated with chiral imines derived from five different chiral, disubstituted, methyl amines. The strongest matched and mismatched reactions with the two enantiomers of the catalyst were noted with disubstituted methyl amines that had one aromatic and one aliphatic substituent. The synthetic scope for the AZ reaction was examined in detail for α-methylbenzyl amine for *cis*-aziridines from α-diazo esters and for *trans*-aziridines from α-diazo acetamides. Optically pure aziridines could be routinely obtained in good yields and with high diastereoselectivity and the minor diastereomer (if any) could be easily separated. The matched case for *cis*-aziridines involved the (*R*)-amine with the (*S*)-ligand, but curiously, for *trans*-aziridines the matched case involved the (*R*)-amine with the (*R*)-ligand for imines derived from benzaldehyde and *n*-butanal, and the (*R*)-amine with the (*S*)-ligand for imines derived from the bulkier aliphatic aldehydes pivaldehyde and cyclohexane carboxaldehyde.

Keywords: asymmetric synthesis · aziridination · aziridines · boroxinate catalyst · homogeneous catalysis

Introduction

Catalysts prepared from either the VANOL or VAPOL ligand and B((OPh)$_3$ have provided a general method for the asymmetric catalytic synthesis of aziridines that involves the reaction of imines and diazo compounds.[1,2] Neither the VANOL or VAPOL ligand will react with B(OPh)$_3$ at room temperature, but upon addition of the imine substrate there is an immediate assembly of the catalyst that has been shown to be a chiral boroxinate of the type **9** (Scheme 1).[3] The catalyst is an ion pair consisting of a boroxinate anion and an iminium cation that results from the protonation of the imine. The efficiency and scope of the catalytic asymmetric aziridination reaction (AZ) has evolved over the years mainly with the identification of the optimal aryl substituents for the diarylmethyl group on the nitrogen in imine **1**.[4] Over the entire range of imines that have been examined, the optical purities of the *cis*-aziridines **3** range from 77 to 99% *ee*; which includes imines derived from electron-rich and electron-poor aromatic aldehydes as well as 1°, 2°, and 3° aliphatic aldehydes.[1c,4] While many reactions give aziridines with 98–99% *ee*, those substrates that give less than ideal asymmetric inductions usually require an optical upgrade of the product by any number of procedures. In an effort to palliate the less than perfect induction for these substrates, we considered investigating the aziridination of imines of the type **4** prepared from chiral amines. Less than complete asymmetric induction imparted by the catalyst in this case would result in the formation of the diastereomers **5** and **6**, which should normally be easier to separate than the two enantiomers of **3**. As long as the double-stereo differentiation in the reactions of imines of the type **4** is significant, facile access to useful quantities of either antipode of *cis*-3-substituted aziridine-2-carboxylate esters should be possible.



Scheme 1.

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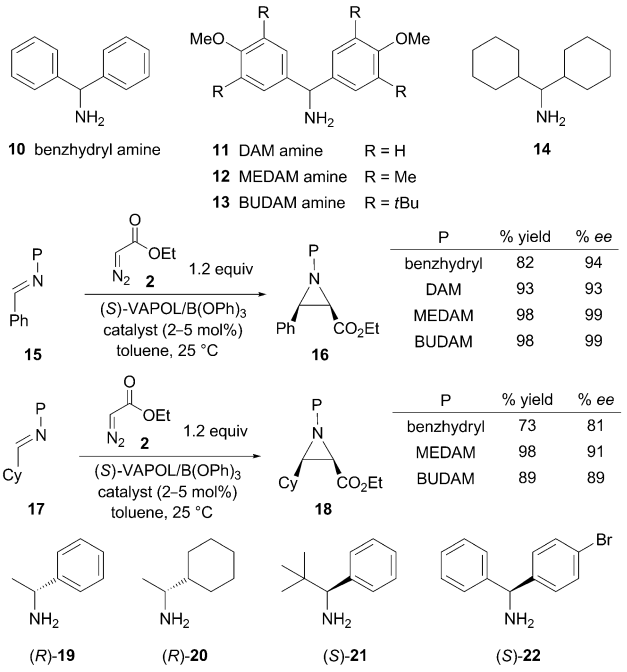
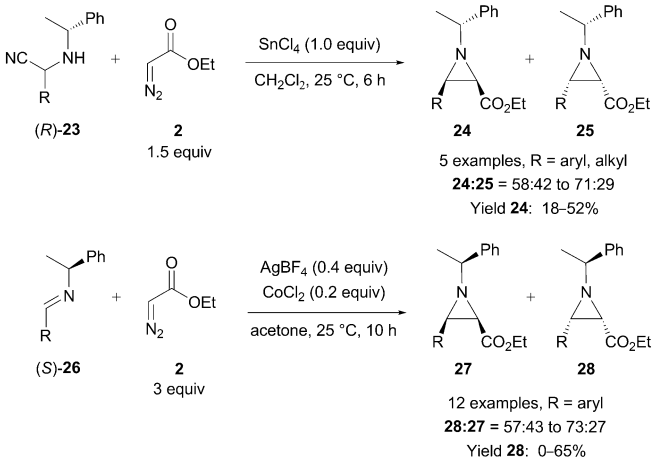


Scheme 2.

Background: The most successful nitrogen substituents on the imine **1** for the catalytic asymmetric aziridination reaction are those that can be generated from the amines **10**–**13** (Scheme 2).[1c,4] A snapshot of the comparison of these amines in the AZ reaction is provided in Scheme 2 for imines **15** and **17**, prepared from benzaldehyde and cyclohexane carboxaldehyde, respectively. These data are a proper reflection of the observed trends. The MEDAM and BUDAM imines give very high asymmetric inductions for imines derived from aryl aldehydes, but they give lower inductions with imines from aliphatic aldehydes.[4b,c] They also give higher asymmetric inductions than benzhydryl imines derived from all classes of aldehydes. However, since the MEDAM and BUDAM amines **12** and **13** are not commercially available, in many cases the most practical approach to aziridines of high optical purity with this method is to perform the aziridination with benzhydryl imines followed by an upgrade of the optical purity of the aziridine product by crystallization, extraction, or chemical conversion.

The set of chiral amines that we chose to examine in the double stereodifferentiation study outlined in Scheme 1 are the four amines **19**–**22** shown in Scheme 2. These were chosen to examine the effect of competition between aryl and alkyl groups, between aryl groups of different electron density, and between two alkyl groups of different size. While two aryl groups on the methyl amine is ideal for the aziridination reaction (**10**–**13**, Scheme 2), two alkyl groups proved to be detrimental. The imine prepared from the *bis*-cyclohexylmethyl amine **14** and benzaldehyde reacts 20 times slower than the corresponding benzhydryl imine and the asymmetric induction drops from 89 to 74% *ee* (in CH_2Cl_2).[4b] Thus we know that two aryl groups provide for efficient aziridination, but we do not know if one aryl group and one alkyl group will give reasonable rates and selectivities, since unsymmetrically disubstituted methyl imines of the type **4** (Scheme 1) have not been previously investigated.

The aziridinations of chiral imines of the type **4** with diazo compounds have not been previously investigated with chiral catalysts; however, three reports have appeared that describe these reactions with nonchiral catalysts.[5] Two of the more thorough studies are summarized in Scheme 3.



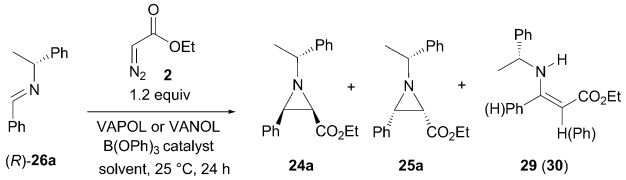
Scheme 3.

Ha and Lee and co-workers generated imines of the type **4** in-situ during the Lewis acid mediated aziridination of α-amino nitriles **23** derived from (*R*)-α-methylbenzyl amine (*R*)-**19** with ethyl diazoacetate.[5b] The optimal conditions involved reaction with one equivalent of tin tetrachloride and gave a mixture of diastereomeric aziridines **24** and **25**, whereby the former predominated in ratios ranging from 58:42 to 71:29. Both aryl and alkyl substituents could be introduced into the aziridine in the 3-position and the yields of the major diastereomer **24** ranged from 18–52%. Lee and co-workers found that the imines (*S*)-**26** could be directly induce to react with ethyl diazoacetate by a combination of 20 mol% cobalt chloride and 40 mol% silver tetrafluoroborate to give a mixture of the diastereomers **27** and **28** in ratios favoring **28** ranging from 57:43 to 73:27 with yields of **28** ranging from 0–65%.[5c] This study only examined imines generated from aryl aldehydes. To summarize previous studies, imines generated from α-methylbenzyl amine give a slight diastereomeric preference for a particular diastereomer, the relative stereochemistry of which is independent of the nature of the nonchiral Lewis acid. The degree of the stereoselection is low and the yields of aziridines produced are not generally useful.

Results and Discussion

Double stereodifferentiation with amines 19–22: The initial screen of chiral imines was carried out with the imine **26a**

Table 1. Matched and mismatched aziridinations of the phenethyl imine (*R*)-**26a**.[a]



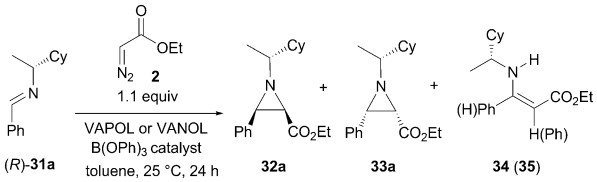
	Ligand	Solvent	*t* [h]	Conv. [%]	**24a**:**25a**[b]	Yield **24a** [%][c]	Yield **25a** [%][c]	Yield **29**/**30** [%][d]
1	(*S*)-VAPOL	CCl_4	24	100	>98:2	79	<2	2/2
2	(*R*)-VAPOL	CCl_4	24	100	33:67	20[d]	40	27/17
3	(*S*)-VANOL	CCl_4	24	100	>98:2	86	<2	4/3
4	(*R*)-VANOL	CCl_4	24	100	31:69	18[d]	26	33/19
5	$B(OPh)_3$ only	CCl_4	24	100	86:14	nd	nd	nd
6	(*S*)-VAPOL	toluene	1	87	97:3	52	2[d]	4/6
7	(*R*)-VAPOL	toluene	1	82	41:59	18	26[d]	3/8
8	(*S*)-VAPOL	toluene	24	100	96:4	74	3[d]	1/7
9	(*R*)-VAPOL	toluene	24	100	33:67	17	33[e]	7/11
10	(*S*)-VANOL	toluene	24	100	>97:3	69	<2[d]	3/3
11	(*R*)-VANOL	toluene	24	100	31:69	22	48[d]	9/15
12	$B(OPh)_3$ only	toluene	24	66	75:25	31	10[d]	7/8

[a] Unless otherwise specified all reactions were run at 0.5 M in imine with 1.1–1.2 equivalents of **2** and 10 mol% catalyst. The *cis:trans* selectivity was >50:1 in all cases. The catalyst for the reactions in CCl_4 was prepared from 1 equivalent of the ligand and 3 equivalent of $B(OPh)_3$ according to Method A in the Experimental Section given in the Supporting Information (entries 1–4), and the catalyst for the reactions in toluene was prepared from 1 equivalent of the ligand, 4 equivalent of $B(OPh)_3$ and 1 equivalent H_2O according to Method B in the Experimental Section given in the Supporting Information (entries 6–12). Imine (*R*)-**26a** was prepared from an imine of >99% *ee* and is an oil and was purified by distillation prior to use. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield after chromatography on silica gel. [d] Yield from ^1H NMR spectrum of the crude reaction mixture based on the isolated yield of **24a** or **25a**. [e] Yield by ^1H NMR is 34%.

derived from the (*R*)-enantiomer of α-methylbenzyl amine **19**. The reactions of this imine with ethyl diazoacetate **2** were carried out with catalysts derived from both the VANOL and VAPOL ligands and in both CCl_4 and toluene as solvents with the results presented in Table 1. There is an inherent preference for this chiral imine to give diastereomer **24a** with the nonchiral catalyst $B(OPh)_3$, which provides an 86:14 selectivity in CCl_4 and a 75:25 selectivity in toluene (Table 1, entries 5 and 10). The results from Table 1 definitely show that there is a synergism between the chiral centers in the imine and in the catalyst with the matched case resulting from the reaction of the (*R*)-enantiomer of imine **26a** and the (*S*)-enantiomer of the ligand. In the matched case, the stereoselectivity is ≥25:1 in favor of **24a** over **25a** for both ligands and in both solvents (Table 1, entries 1, 3, 8, and 10). The mismatched cases result from the reaction of the (*R*)-enantiomer of the imine **26a** with the (*R*)-enantiomer of the ligand. The catalyst derived from the (*R*)-ligand is able to flip the diastereoselection in favor of diastereomer **25a** but only by a factor of approximately two and again this is true for both ligands and for both solvents (Table 1, entries 2, 4, 9, and 11). The total yields of aziridine products drops in the mismatched cases and the mass balance is largely made up for by the formation of the enamine products **29** and **30**. In all cases, no *trans* isomers of **24a** or **25a** could be detected in the ^1H NMR spectra of crude reaction mixtures, as indicated by the absence of doublets with the proper coupling constants ($J \approx 3$ Hz) for the methine protons for a *trans*-aziridine. A *cis/trans* selectivity of >50:1 can be assigned in all cases. The assignment of the relative stereochemistry in aziridine **24a** was made after comparison of its rotation with that reported in the literature for this compound[5b] and by its conversion to the (*R*)-enantiomer of phenylalanine ethyl ester **49** (Scheme 6, see below). The standard reaction time for these reactions was 24 h, but no effort was made to determine the minimum reaction times, which are undoubtedly significantly less than 24 h since reactions stopped after 1 h are 82–87% complete (Table 1, entries 6 and 7).

The catalytic aziridination of the cyclohexylethyl imine **31a** pits the effects of a cyclohexyl group versus a methyl group in vying for the diastereoselection in competition with the VAPOL and VANOL catalysts. It turns out that these effects appear to be small as there is very little difference in the selectivities seen with the (*R*)- or (*S*)-enantiomers of either ligand (Table 2). This is also true with the nonchiral catalyst

Table 2. Matched and mismatched aziridinations of the cyclohexylethyl imine (*R*)-**31a**.[a]



	Ligand	Conv. [%]	**32a**:**33a**[b]	Yield **32a** [%][c]	Yield **33a** [%][d]	Yield **34**/**35** [%][d]
1	(*S*)-VAPOL	90	83:17	35	6	3/7
2	(*R*)-VAPOL	66	20:80	7	28	3/5
3	(*S*)-VANOL	64	83:17	32	5	2/4
4	(*R*)-VANOL	100	25:75	15	45	4/9
5	$B(OPh)_3$ only	38	56:44	nd	nd	nd

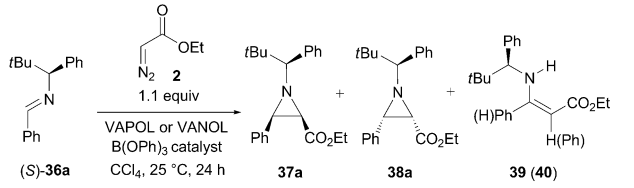
[a] Unless otherwise specified all reactions were run at 0.5 M in imine with 1.2 equivalents of **2** and 10 mol% catalyst at room temperature for 24 h. The *cis:trans* selectivity was >50:1 in all cases. The catalyst for the reactions was prepared from 1 equivalent of the ligand, 4 equivalents of $B(OPh)_3$ and 1 equivalent H_2O according to Method B in the Experimental Section in the Supporting Information. nd = not determined. Imine (*R*)-**31a** was an oil and used without purification after being prepared from the corresponding amine with >99% *ee*. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield after chromatography on silica gel. [d] Yield from ^1H NMR spectrum of the crude reaction mixture based on the isolated yield of **32a**.

$B(OPh)_3$ which gives nearly a 1:1 ratio of the diastereomers **32a** and **33a** (Table 2, entry 5). The selectivity imparted by the ligands is 5:1 in favor of **32a** with the (*S*)-enantiomers of VANOL and VAPOL (Table 2, entries 1 and 3) and 3–4:1 in favor of **33a** with the (*R*)-enantiomers of the ligands (entries 2 and 4). The relative stereochemistry of **32a** and **33a** were not assigned, but rather assumed to correlate with **24a** and **25a**. The total mass balance of these reactions for the two diastereomers together is only 35–60%, which translates to 45–60% if the percent conversion for the reaction is taken into account. The remainder of the material balance was not determined, except for the small amounts of the enamine products that were detected in the ^1H NMR spectrum of the crude reaction mixture. It was noted that the reaction of the imine **31a** was not complete in 24 h with either the (*S*)-VAPOL- or (*R*)-VAPOL-derived catalysts. This is in contrast to the corresponding aromatic analogue **26a** in which the reaction reaches the same degree of completion in 1 h for both the matched and mismatched cases (Table 1, entries 6 and 7). This is consistent with the fact that the aziridination with the imine derived from the all aliphatic amine **14** and benzaldehyde is twenty five times slower than the corresponding imine derived from the aromatic benzhydryl amine **10**.[4b]

The aziridination of the imine **36a** puts a *tert*-butyl group up against a phenyl group in the control of diastereoselectivity in reaction with ethyl diazoacetate. As can be seen from the data in Table 3, there are significantly disparate effects between the (*R*)- and (*S*)-enantiomers for both the VAPOL and VANOL ligands. The matched case is the same as with the α-methylbenzyl imine **26a** in which the (*S*)-enantiomer of the imine is matched with the (*R*)-enantiomer of the ligand (*R* with *S* and *S* with *R*). No detectable amount of the diastereomer **37a** was formed in the reaction of (*S*)-**36a** with either the (*R*)-VAPOL or (*R*)-VANOL catalysts, both of which give the aziridine product as a single diastereomer **38a** in 80–85% yield. This is a slightly stronger matched/mismatched pair than seen in the reactions of the α-methylbenzyl imine **26a**. The selectivity flips over for the mismatched case with the (*S*)-VAPOL catalyst giving a 69:31 preference for the **37a** over **38a**, but the (*S*)-VANOL gives an essentially equal mixture of the two. This is also reflected in the fact that the nonchiral catalyst $B(OPh)_3$ gives a strong selectivity in favor of the matched diastereomer (92:8). The major product **37a** from the mismatched reaction of the imine (*S*)-**36a** with (*S*)-VAPOL was crystalline and the relative stereochemistry of **37a** was determined by X-ray diffraction.

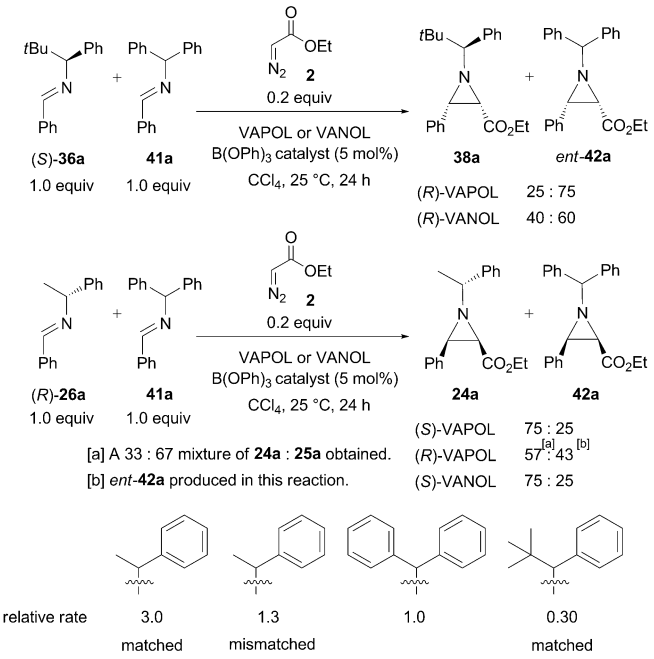
With the finding that both the α-methylbenzyl imine **26a** and the α-*tert*-butylbenzyl imine **36a** have strong matched and mismatched relationships with the VANOL and VAPOL ligands, it was decided to investigate how the rates of these reactions compare with the corresponding benzhydryl imine **41a**. These experiments were conducted by performing pair-wise reactions between equimolar amounts of two substrates with a deficiency of ethyl diazoacetate, such that the reactions stops at 20% conversion at which point the ratio of the two products is determined. By this measure, the reaction of the α-*tert*-butylbenzyl imine **36a** in the matched case is a factor of three slower than the benzhydryl imine **41a** (Scheme 4). Interestingly, the α-methylbenzyl imine **26a** is three times faster than the benzhydryl imine **41a** in the matched case. A similar experiment reveals that the α-methylbenzyl imine **26a** is 1.3 times faster than the benzhydryl imine **41a** in the mismatched case. Thus, the re-

Table 3. Matched and mismatched aziridinations of the phenylneopentyl imine (*S*)-**36a**.[a]



	Ligand	**37a**:**38a**[b]	Yield **37a** [%][c]	Yield **38a** [%][d]	Yield **39**/**40** [%][d]
1	(*S*)-VAPOL	69:31	56	25	nd
2	(*R*)-VAPOL	<2:98	<2[d]	80[c]	<2
3	(*S*)-VANOL	52:48	36	33	11/2
4	(*R*)-VANOL	<2:98	<2[d]	85[c]	<2
5	$B(OPh)_3$ only	8:92	nd	nd	24/11

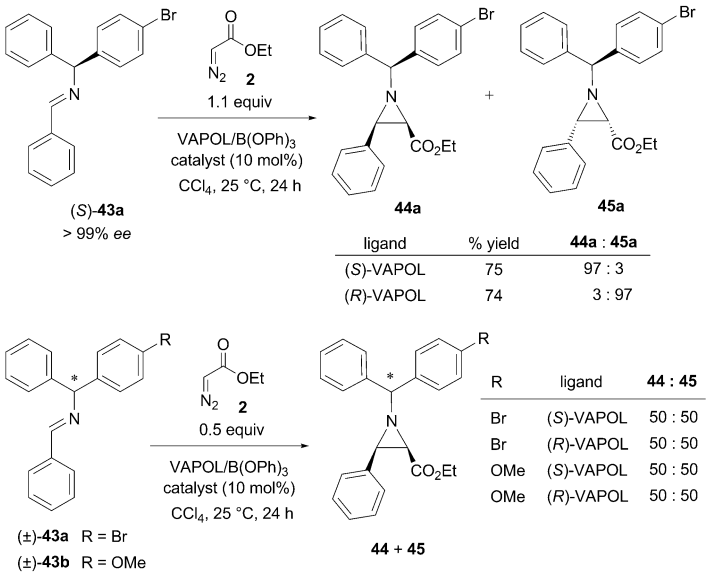
[a] Unless otherwise specified all reactions were run at 0.5 M in imine with 1.1 equivalents of **2** and 10 mol% catalyst at room temperature for 24 h. The *cis*:*trans* selectivity was >50:1 in all cases. The catalyst for the reactions was prepared from 1 equivalent of the ligand, 3 equivalents of $B(OPh)_3$ according to Method A in the Experimental Section in the Supporting Information. nd = not determined. Imine (*S*)-**36a** was purified by crystallization and was prepared from an amine of greater than 99.5% *ee*. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield after chromatography on silica gel. [d] Yield from ^1H NMR spectrum of the crude reaction mixture based on the isolated yield of **37a** or **38a**.



Scheme 4.

action of the α-methylbenzyl imine **26a** in the matched case is 2.3 times faster than the same reaction in the mismatched case. This is consistent with the slightly greater reaction progress noted for the matched reaction when the reaction of the imine (*R*)-**26a** was stopped after 1 h (Table 1, entries 6 and 7).

As indicated by the data in Scheme 5, chiral benzhydryl substituents provide absolutely no resistance to the catalyst



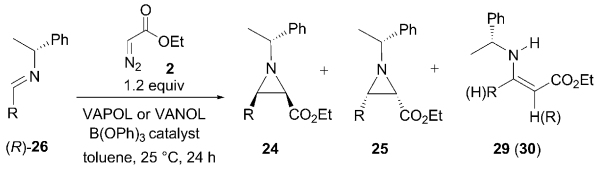
Scheme 5.

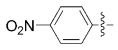
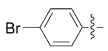
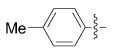
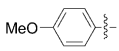
that dominates these reactions with complete catalyst control. The reaction of the imine (*S*)-**43a** (>99% *ee*) with a phenyl and a *p*-bromophenyl substituent gave a 97:3 mixture of **44a** to **45a** in favor of **44a** with the (*S*)-VAPOL catalyst and a 3:97 mixture with the (*R*)-VAPOL catalyst. The fact that the *p*-bromo substituent has no effect at all and that the matched and mismatched reactions both give a 97:3 selectivity is consistent with the fact that the benzhydryl imine **41a** will react with ethyl diazoacetate to give aziridine **42a** in 93% *ee* (96.5:3.5 e.r.) in carbon tetrachloride as solvent.[1c] On this basis the relative stereochemistry of **44a** and **45a** were assigned such that the 2*R*,3*R* isomer is produced by the *S* enantiomer of the ligand, as is the case for the reaction of imine **41a**. An alternative method for probing for matched and mismatched effects is to look for their manifestation in kinetic resolution experiments. This was examined for the racemic benzhydryl imines **43a** and **43b**, bearing *p*-bromo and *p*-methoxy substituents, respectively. The reaction of the racemic *p*-bromophenyl imine **43a** with 0.5 equivalents of ethyl diazoacetate gave a 50:50 mixture of the diastereomers **44** and **45**. This is consistent with the reactions of the optically pure imine **43a** with catalysts from (*S*)- and (*R*)-VAPOL. Exactly the same results were obtained with the racemic *p*-methoxy imine **43b** and thus it is clear that electronic differences in the two phenyl groups of the benzhydryl unit on the imine do not have any influence on the stereoselectivity in the aziridination reaction. This result was a little unexpected, since it was observed by X-ray analysis that the binding of the imine substrate in the VAPOL catalyst **9** results from different types of interactions for the two phenyl groups.[3b] However, it should be noted that in computational studies on the transition states for the aziridination reaction that these types of interactions of the phenyl groups with the catalyst do not exist.[6]

Substrate scope for *cis*-aziridines with α-methylbenzyl imine 26: With regard to the selection of a chiral auxiliary, it was decided to move forward with the α-methylbenzyl amine **19** (Scheme 2). The α-*tert*-butylbenzyl amine **21** was shown to give slightly higher diastereoselectivities in reactions of its imine from benzaldehyde (Table 3) than the corresponding imine from amine **19** (Table 1); however, the α-*tert*-butylbenzyl amine **21** is not commercially available. Both enantiomers of the α-methylbenzyl amine **19** are commercially available and, furthermore, both enantiomers are roughly the same price as the benzhydryl amine **10**. The diastereoselectivity for the aziridination of the imine **26a** are very high and the two diastereomers **24a** and **25a** are easy to separate by column chromatography (Table 1). The isolated yields of the major diastereomer **24a** are also very high (86%). Even though the yields and diastereoselectivities are slightly higher in CCl_4 than in toluene, it was decided to examine the scope of the reaction with imines from other aldehydes in toluene as solvent for reasons of cost and safety. With the VANOL catalyst in toluene the diastereomer **24a** was the exclusive product with no detectable amount of the diastereomer **25a** (Table 1, entry 10).

The scope of the aziridination of imines from α-methylbenzyl amine **19** was explored with five additional aromatic aldehydes and with three aliphatic aldehydes and the results are summarized in Table 4. The imines **26c** and **26d** are solids and were purified by crystallization prior to use. All of the rest of the imines in Table 4 are oils and were used without purification directly after they were prepared. The optimal results for the *para*-nitrophenyl imine (*R*)-**26b** is with (*S*)-VANOL, which gives the diastereomeric aziridine **24b** in 90% isolated yield along with 4% of the diastereomer **25b**, which could be easily be separated by chromatography on silica gel (Table 4, entry 3). A similar situation was found with the *para*-bromophenyl imine (*R*)-**26c** for which the strongest matched case was found with the (*S*)-VANOL ligand giving a 97:3 mixture of aziridines **24c** and **25c**, which were easily separated to give **24c** in 77% yield (Table 4, entry 8). Both ligands were equally effective in the aziridination of the *para*-methylphenyl imine (*R*)-**26d** with the isolation of the matched imine **24d** in 70–71% yield with no detectable amount of the diastereomer **25d** formed in either reaction (Table 4, entries 11 and 13). A dramatic difference between the two ligands was observed with the *para*-methoxyphenyl imine (*R*)-**26e**, for which even for the matched case the (*S*)-VAPOL catalyst only goes to 46% completion, while the (*S*)-VANOL catalyst goes to completion and provides a 63% isolated yield of the pure aziridine **24e**

Table 4. Matched and mismatched aziridinations of the phenethyl imines (*R*)-**26**.[a]



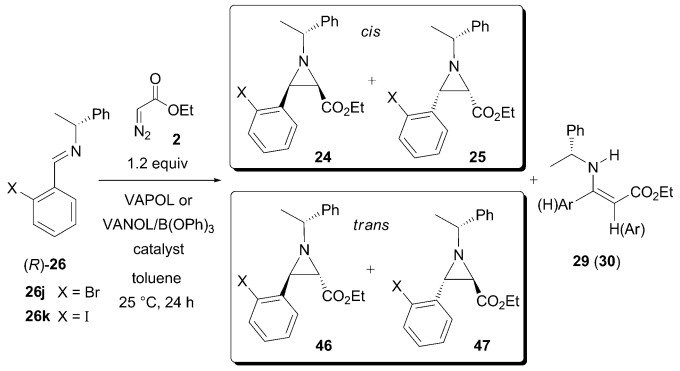
	R	Ligand	Conv. [%]	**24**:**25**[b]	Yield **24** [%][c]	Yield **25** [%][d]	Yield **29**/**30** [%][d]
1	 (*R*)-**26b**	(*S*)-VAPOL	100	94:6	74	4	4/5
2		(*R*)-VAPOL	100	33:67	19	38	12/14
3		(*S*)-VANOL	100	96:4	90	3	4/3
4		(*R*)-VANOL	100	33:67	19	38	12/14
5		$B(OPh)_3$ only	100	71:29	31	12	5/7
6	 (*R*)-**26c**	(*S*)-VAPOL	100	94:6	82	5	4/4
7		(*R*)-VAPOL	100	38:62	24	40[e]	13/13
8		(*S*)-VANOL	100	97:3	77	2	11/9
9		(*R*)-VANOL	100	31:69	21	46	9/9
10		$B(OPh)_3$ only	94	77:23	35	10	11/8
11	 (*R*)-**26d**	(*S*)-VAPOL	100	>98:2	71	<1	0/1
12		(*R*)-VAPOL	100	33:67	19	38[f]	3/7
13		(*S*)-VANOL	100	>98:2	70	<1	3/13
14		(*R*)-VANOL	100	38:62	21	35	6/8
15		$B(OPh)_3$ only	61	80:20	28	7	4/3
16	 (*R*)-**26e**	(*S*)-VAPOL	46	95:5	35	2	3/5
17		(*R*)-VAPOL	21	47:53	nd	nd	nd
18		(*S*)-VANOL	100	98:2	63	1	7/23
19		(*R*)-VANOL	29	44:56	nd	nd	nd
20		$B(OPh)_3$ only	8	nd	nd	nd	nd
21	 (*R*)-**26f**	(*S*)-VAPOL	100	>98:2	62	<1	1/0
22		(*R*)-VAPOL	100	41:59	23	16	15/0
23		(*S*)-VANOL	100	>98:2	52	<1	9/6
24		(*R*)-VANOL	100	44:56	16	13	11/0
25		$B(OPh)_3$ only	28	75:25	<21	<7	<15/<27
26	 (*R*)-**26g**	(*S*)-VAPOL	100	83:17	66	13	0/0
27		(*R*)-VAPOL	100	23:77	14	47	0/0
28		(*S*)-VANOL	100	83:17	72	14	0/0
29		(*R*)-VANOL	100	23:77	23	76	0/0
30		$B(OPh)_3$ only	53	55:45	17	21	0/0
31	 (*R*)-**26h**	(*S*)-VAPOL	100	91:9	61	6	0/0
32		(*R*)-VAPOL	31	38:62	13	22[g]	0/0
33		(*S*)-VANOL	100	93:7	79	6	0/0
34		(*R*)-VANOL	100	41:59	22	31	0/0
35		$B(OPh)_3$ only	43	58:42	18	13	0/0
36	 (*R*)-**26i**	(*S*)-VANOL	100	80:20	28[h]	7	0/0
37		(*R*)-VANOL	100	47:53	29[i]	33	0/0

[a] Unless otherwise stated all reactions were run at 0.5 M in imine with 1.2 equivalents of **2** and 10 mol% catalyst in toluene at room temperature for 24 h. The catalyst was prepared from 1.0 equivalent of the ligand, 4.0 equivalents of $B(OPh)_3$ and 1.0 equivalent H_2O according to Method B in the Experimental Section in the Supporting Information. nd = not determined. Imine (*R*)-**26c** and (*R*)-**26d** were purified by crystallization. All other imines were oils and used without purification. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture [c] Isolated yield after chromatography on silica gel. [d] Yield from ^1H NMR spectrum of the crude reaction mixture based on the isolated yield of **24**. [e] Isolated yield is 27%. [f] Isolated yield is 32%. [g] Isolated yield is 20%. [h] Yield from ^1H NMR spectrum is 41% with Ph_3CH as internal standard. [i] Yield determined from ^1H NMR spectrum with Ph_3CH as internal standard.

(Table 4, entry 18). Note that both catalysts are very slow in the mismatched cases giving 21 and 29% conversion under the same conditions (Table 4, entries 17 and 19). A single diastereomer of the *ortho*-methylphenyl aziridine **24f** is produced in the reactions of the corresponding imine (*R*)-**26f** with catalysts from both ligands with a higher yield registered with the (*S*)-VAPOL catalyst (Table 4, entry 21). The weakest matched and mismatched relationship was found for the imine (*R*)-**26g** derived from cyclohexane carboxaldehyde. In fact the diastereoselectivity is nearly equal with the (*S*)- and (*R*)-ligands (83:17 vs 23:77) and thus this is more a case of catalyst control rather than substrate control. The diastereomers **24g** and **25g** are easy to separate and a greater than 70% yield of either pure diastereomer can be obtained with the proper choice of the chirality of the VANOL ligand (Table 4, entries 28 and 29). The imine (*R*)-**26h** derived from *tert*-butyl carboxaldehyde gives a matched and mismatched relationship with both VANOL and VAPOL that is more closely related to aryl aldehydes than to cyclohexane carboxaldehyde. A 93:7 selectivity in favor of aziridine **24h** is observed for the matched case with the (*S*)-VANOL catalyst resulting in a 79% isolated yield of the pure aziridine. The imine (*R*)-**26i** prepared from the α-unbranched aldehyde *n*-butanal, reacted to give low yields of the aziridines **24i** and **25i**. Even in the matched case with a 80:20 ratio of **24i** to **25i**, the aziridine **24i** could only be isolated in 28% yield. It is interesting to note that the same imine will react with the diazoacetamide **51** to give a *trans*-aziridines **53i** (Table 7, see below) in much greater yields. The causes of the low yields for imine **26i** may be related to those responsible for low yields in the aziridination of imines derived from the DAM amine **11** and *n*-butanal.[4c] Finally, the reactions catalyzed by $B(OPh)_3$ tend to give low yields and selectivities in the range of 55:45–80:20 which is very similar to those observed for the nonchiral Lewis acids $SnCl_4$ and $CoCl_2$ (Scheme 3).

In all of the aziridination reactions of imines **26** investigated up to this point (Tables 1 and 4) the products have been exclusively the *cis* isomers of the diastereomeric aziridines **24** and **25**. Deviant from these observations are the reactions of imines **26** derived from *ortho*-halo-benzaldehydes

Table 5. Matched and mismatched aziridinations of the *o*-bromo- and iodophenyl imines (*R*)-**26**.[a]

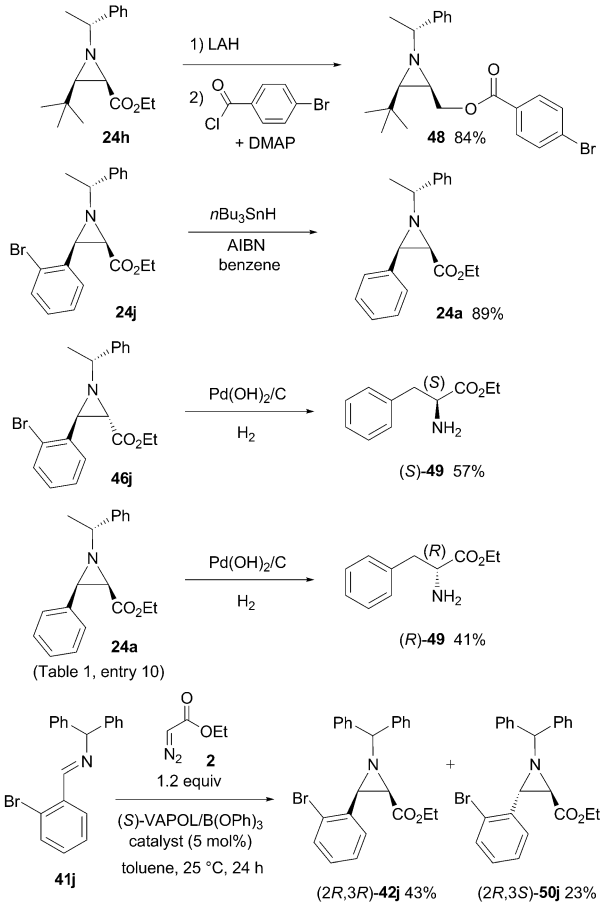


	X	Ligand	Yield **24** [%][b]	Yield **25** [%][c]	Yield **46** [%][d]	Yield **47** [%][c]	*cis*/*trans*	**24**:**25**	**46**:**47**	Yield **29**/**30** [%][c]
1	Br	(*S*)-VAPOL	48	5	14	7	71:29	91:9	67:33	10/16
2	Br	(*R*)-VAPOL	10	10	33	3	35:65	50:50	93:7	15/21
3	Br	(*S*)-VANOL	43	1	8	11	70:30	97:3	44:56	10/12
4	Br	(*R*)-VANOL	10	8	30	2	36:64	55:45	92:8	10/13
5	Br	$B(OPh)_3$ only	13	4	50	7	23:77	75:25	88:12	13/13
6	I	(*S*)-VAPOL	21	1	15	7	50:50	94:6	67:33	11/17
7	I	(*R*)-VAPOL	8	8	40	4	26:74	50:50	91:9	15/21
8	I	(*S*)-VANOL	23	1	15	7	52:48	96:4	67:33	10/12
9	I	(*R*)-VANOL	7	4	30	3	25:75	63:37	91:9	10/13
10[e]	I	$B(OPh)_3$ only	6	12	51	9	23:77	33:67	85:15	11/11

[a] Unless otherwise specified all reactions were run at 0.5 M in imine with 1.2 equivalents of **2** and 10 mol% catalyst at room temperature for 24 h and went to 100% completion. The catalyst for the reactions was prepared from 1 equivalent of the ligand, 4 equivalents of $B(OPh)_3$ and 1 equivalent H_2O according to Method B in the Experimental Section in the Supporting Information. Imine (*R*)-**26j** and (*R*)-**26k** were oils and used without purification. [b] Isolated yield of **24j** after chromatography on silica gel. The yields of **24k** were determined from ^{1}H NMR spectrum of the crude reaction mixture and based on the isolated yield of **46k**. [c] Yield from ^{1}H NMR spectrum of the crude mixture and based on the isolated yield of **24j** or **46k**. [d] Isolated yield of **46k** after column chromatography on silica gel. The yield of **46j** were determined from the ^{1}H NMR spectrum of the crude mixture and are based on the isolated yield of **24j**. [e] The reaction went to 80% completion.

(Table 5). The *ortho*-bromo and *ortho*-iodo derivatives **26j** and **26k** give mixtures of all four possible diastereomers. As was seen with all of the other reactions of imines **26** producing *cis*-aziridines, the matched case for the (*R*)-enantiomers of **26j** and **26k** is with the (*S*)-enantiomers of VANOL and VAPOL catalysts. For example, the reaction of (*R*)-**26j** with the (*S*)-VANOL catalyst gives a 97:3 selectivity for the *cis* diastereomer **24j** over the *cis* diastereomer **25j** with a total *cis*:*trans* selectivity of 70:30. It was interesting to observe that the matched cases for the *trans*-aziridines **46** and **47** are the mismatched cases for the *cis*-aziridines **24** and **25**. The reaction of the (*R*)-enantiomer of **26k** with the (*R*)-VANOL catalyst gives a 92:8 mixture of the *trans* diastereomers **46k** and **47k** with a total *trans*:*cis* selectivity of 64:36. In the matched reactions of **26j** for the formation of both the *cis* and *trans* diastereomers (**24** and **46**), facial selectivity for the reaction of the imine is the same, but that for the diazo compound is changed. Very similar reaction patterns were seen for the reactions of the *ortho*-iodo imine **26k** with the exception that the yields tended to be a little lower for the *cis*-aziridines in the matched case.

The relative stereochemistry of the *cis*-aziridines **24** with an aryl substituent R shown in Table 4 was assumed to be the same as that determined for the phenyl aziridine **24a** (Table 1). The relative stereochemistry of the cyclohexyl aziridine **24g** was assigned by a chemical correlation with the known aziridine **62g**[4a] as outlined in Scheme 9 (see below). The assignment of the relative stereochemistry for the *tert*-butyl-substituted aziridine **24h** was made by conversion to the *p*-bromobenzoate **48**, which was a solid that gave crystals suitable for X-ray analysis (Scheme 6). The stereochemistry of the *n*-propyl aziridine **24i** was assumed to be the same as the phenyl, cyclohexyl and *tert*-butyl analogues. The relative stereochemistry of the *cis*- and *trans*-isomers **24j** and **46j** was determined as outlined in Scheme 6. Tin hydride reduction of the **24j** gives an 89% yield of aziridine **24a**, a compound that was found to be identical with the aziridine formed from the reaction of imine (*R*)-**26a** in the matched case with (*S*)-VAPOL (Table 1, entry 1). The assignment of the relative stereochemistry for the *trans*-aziridine **46j** was determined by hydrogenation with Pearlman's catalyst, which resulted in the reduction of the bromide, reductive ring-opening of the aziridine, and reductive cleavage of the α-methylbenzyl group on the nitrogen. The resulting ethyl ester of phenyl alanine **49** was found to have the *S* configuration by comparing its rotation to that of the known compound.[1a] Similar treatment of **24a** obtained as the major diastereomer from the reaction of imine (*R*)-**26a** in the matched case with (*S*)-VAPOL (Table 1) gave the (*R*)-enantiomer of phenylalanine ethyl ester, which reveals that the *cis*-aziridine **24a** (and thus *cis*-aziridine **24j**) and the *trans*-aziridine **46j** differ in the configuration at C2. It was assumed that the relative stereochemistry of the *ortho*-iodophenyl aziridines **24k** and **46k** is the same as that for the corresponding *ortho*-bromophenyl aziridines. The aziridination of the *ortho*-bromophenyl imine **41j** derived from benzhydryl amine has been previously shown to give a 1.9:1 mixture of the *cis*- and *trans*-aziridines (Scheme 6).[1c] It was later shown that the absolute stereochemistry of the *cis*-isomer **42j** is (2*S*,3*S*) and that of the *trans*-isomer **50j** is (2*R*,3*S*).[7] It is of interest to note that the while the matched *cis*-aziridine **24** differs from the matched *trans*-aziridine **46** by the configuration at C2 (Table 5), the *cis*- and *trans*-aziridines **42j** and **50j** from the

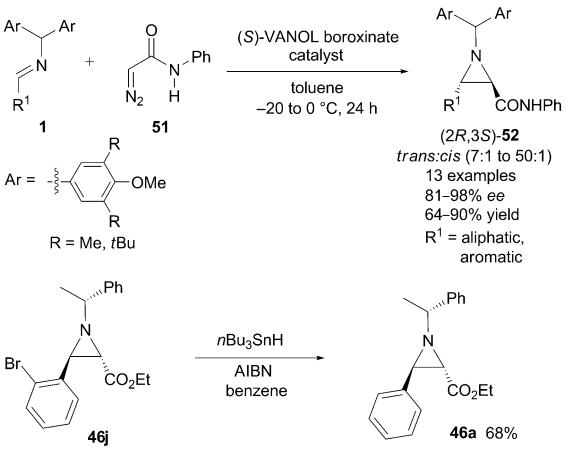


Scheme 6.

nonchiral imine **41j** differ by the configuration at C-3 (Scheme 6).

***trans*-Aziridines from α-methylbenzyl imines 26 and diazoacetamides**: The origin of the formation of substantial proportions of *trans*-aziridines from imines **26j** and **26k** that bear an *ortho*-halogen substituent (Table 5) is not understood at this time, but it is clear that this is not due to just the presence of an *ortho*-substituent, since the *ortho*-methylphenyl imine **26f** does not give an detectable amount of the *trans*-aziridine (Table 4, entries 21–25). What is perhaps better understood is the reason that *sec*-diazoacetamides of the type **51** give *trans*-aziridines (Scheme 7).[6,7] This switch in diastereoselectivity from *cis* for the diazo ester **2** (Scheme 1) to *trans* for the diazoacetamide **51** has been attributed to the ability of the N–H bond of the **51** to participate in a hydrogen bond to the anionic boroxinate core of the VANOL catalyst **9** (Scheme 1).[6] The *trans*-aziridines **52** can be obtained in high yields with excellent enantioselectivities for imines derived from both aliphatic and aromatic aldehydes.[7]

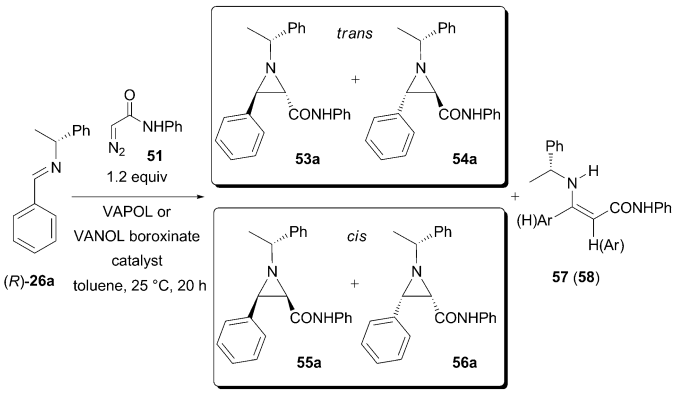
Access to diastereomerically and enantioselectively pure *trans*-aziridines via α-methylbenzyl imines can be expanded beyond *ortho*-halophenyl imines, since the *ortho*-bromo substituent in the *trans*-aziridine **46j** can be reduced with tributyl tin hydride without opening the aziridine ring to give the *trans*-aziridine **46a** in 68% yield (Scheme 7), an aziridine which is not observed in the reaction of imine (*R*)-**26a** (Table 1). However, the usefulness of this approach is limited not only by the fact that other reducible functional groups cannot be present, but also by the fact that the *trans*-α-halophenyl aziridines can only be obtained in low yields (30–50%) even in the matched case (Table 5).



Scheme 7.

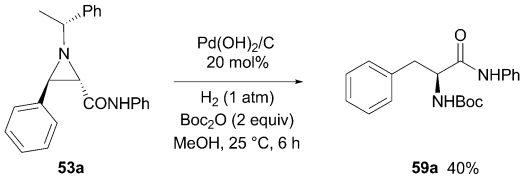
The most practical approach to *trans*-aziridines using the double stereodifferentiation approach would be if the reactions of α-methylbenzyl imines with diazoacetamides were themselves *trans*-selective as are the reactions of nonchiral imines. That this is the case, is shown by the data in Table 6, which presents the results of the aziridination of the imine (*R*)-**26a** with the diazoacetamide **51**. The VAPOL catalyst gives a 88:12 ratio of the *trans* to *cis* isomers with a 91:9 mixture of the two *trans* diastereomers **53a** and **54a**. The relative stereochemistry of major diastereomer **53a** produced from the reaction of (*R*)-**26a** with the (*R*)-VANOL or (*R*)-VAPOL catalyst was established by the reductive ring-opening to give the phenyl alanine derivative **59a** of known optical rotation (Scheme 8).[8] As is the case for the formation of the *trans* isomers from the α-halophenyl imines **23j** and **23k**, the matched reaction is that of the (*R*)-imine with the (*R*)-VAPOL ligand. The VANOL ligand gives a slightly better profile with an 89:11 *trans* to *cis* ratio and a 95:5 ratio of the two *trans* diastereomers, although both ligands give the same isolated yield of the *trans* diastereomer **53a** (70–71%). The profile for the VANOL catalyst could be improved by lowering the reaction temperature to 0°C (Table 6, entries 4 versus 5). Here the *trans*:*cis* selectivity is now 96:4 and the selectivity for the *trans* diastereomer **53a** is complete with no detectable amount of **54a** formed. As a consequence of these increased selectivities, the isolated amount of the *trans*-aziridine **53a** is increased from 70 to 78% yield. The relative stereochemistry of the *cis*-aziridine **55a** was determined by its conversion to **24a** (see Supporting Information).

Table 6. Matched and mismatched *trans*-aziridinations of imine (*R*)-**26** with diazoacetamide **51**.[a]



	Ligand	Yield **53a** [%][b]	Yield **54a** [%][c]	Yield **55a** [%][c]	Yield **56a** [%][c]	*trans*/*cis*	**53a**:**54a**	**55a**:**56a**	Yield **57/58** [%][c]
1	(*S*)-VAPOL	25	17	9	2	79:21	60:40	83:17	11/19
2	(*R*)-VAPOL	71	7	5	5	88:12	91:9	50:50	6/6
3	(*S*)-VANOL	28	18	16	6	68:32	62:38	75:25	18/16
4	(*R*)-VANOL	70	4	6	3	89:11	95:5	67:33	8/10
5[d]	(*R*)-VANOL	78	<4	2	1	96:4	>95:5	67:33	3/4
6[e]	(*R*)-VANOL	69	3	4	3	91:9	95:5	60:40	6/9
7	$B(OPh)_3$ only	43	14	8	2	86:14	75:25	75:25	4/4

[a] Unless otherwise specified all reactions were run at 0.5 M in imine with 1.2 equivalents of **51** and 10 mol% catalyst at room temperature for 20 h and went to 100% completion. The catalyst for the reactions was prepared from 1 equivalent of the ligand, 3 equivalents of $BH_3{\cdot}SMe_2$, 2 equivalents PhOH and 3 equivalents H_2O according to Method C in the Experimental Section in the Supporting Information. Imine (*R*)-**26a** (>99% *ee*) is an oil and was purified by distillation prior to use. [b] Isolated yield after chromatography on silica gel. [c] Yield from ^{1}H NMR spectrum of the crude reaction mixture and based on the isolated yield of **53a**. [d] The reaction was run at 0 °C for 24 h. [e] The catalyst was prepared from 1 equivalent of (*R*)-VANOL, 4 equivalents $B(OPh)_3$ and 1 equivalent H_2O according to Method B in the experimental section. [f] This reaction went to 64% completion.

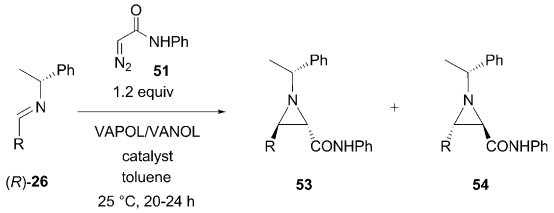


Scheme 8.

Since the asymmetric inductions for the *trans*-aziridines **52** (Scheme 7) derived from aliphatic aldehydes were not generally as high as they were for those from aromatic aldehydes, focus was drawn to the evaluation of α-methylbenzyl imines derived from aliphatic aldehydes and, in particular, the unbranched, α-branched, and α,α-branched examples presented in Table 7. Beginning with the cyclohexyl imine (*R*)-**26g** it was found that very high selectivities (>96:4) were observed for the formation of the *trans* diastereomer **53g** over the *trans* diastereomer **54g** even at 25 °C to provide a 78% isolated yield of **53g** with the VAPOL catalyst and an 80% yield with the VANOL catalyst. This high degree of matched/mismatched stereo double differentiation with the cyclohexyl imine **26g** and the diazo acetamide **51** is surprising, since the same imine with the diazo ester **2** shows an extremely weak matched/mismatched relationship (Table 4). The amount of *cis* diastereomers could not be determined in the reactions in Table 7, because the aliphatic regions of the ^{1}H NMR spectrum of the crude reaction mixtures consisted of many overlapping peaks that prevented the unequivocal identification of their presence. It was of great interest to learn that the matched reaction with the cyclohexyl imine **26g** is of the (*R*)-imine with the (*S*)-ligand, which is opposite to that observed for the phenyl imine **26a** also in the *trans*-aziridination (Table 6). The *tert*-butyl-substituted imine (*R*)-**26h** also gave high selectivities (≥97:3) for the *trans* diastereomer **53h** over the *trans* diastereomer **54h** and its matched case is the same as the cyclohexyl imine **26g**, for which the (*R*)-imine gives the highest selectivity with the (*S*)-ligands. The *tert*-butyl-substituted *trans* diastereomer **53h** was a crystalline compound that provided single crystals that were analyzed by X-ray diffraction to show that the phenyl and *tert*-butyl imines (*R*)-**26a** and (*R*)-**26h** give the same relative stereochemistry in the major diastereomer in the matched cases, even though the matched case with (*R*)-**26a** is with the (*R*)- ligands and for (*R*)-**26h** is with the (*S*)-ligands. The aziridines **53g** and **53i** were assumed to have the same relative stereochemistry as **53a** and **53h** in the matched case. The unbranched aliphatic imine (*R*)-**26i** also gives high stereoselectivity (95:5) for the *trans* diastereomer **53** and surprisingly, its matched case is the same as the phenyl imine **26a** and opposite to cyclohexyl and *tert*-butyl imines **26g** and **26h**. This variation in the matched/mismatched pair with the structure of the imine is unexpected and its meaning is not clear at this time. It is also not clear why the reaction of the *n*-propyl imine (*R*)-**26i** with the diazoacetamide **51** gives the *trans*-aziridine **53i** in excellent yields (79–80%) while reaction of the same imine with ethyl diazoacetate only gives low yields of the *cis*-*n*-propyl aziridine **24i** (Table 4). Nonetheless, it is important that at least one of the diazo compounds gives good yields, since not only are aziridines with unbranched aliphatic groups at the 3- position accessible, but the ring-opening of these aziridines allows access to straight chain α- and β-amino acids derivatives (Scheme 10, see below).

Synthesis of α- and β-amino acid derivatives: The aryl-substituted *cis*-aziridines **24a**, **24d**, and **24f** could be ring-opened with Pearlman's catalyst under one atmosphere of hydrogen in methanol, which also resulted in the cleavage of the α- methylbenzyl group on the nitrogen (Scheme 9). It was found convenient for isolation purposes to perform the reduction in the presence of Boc_2O (Boc = *tert*-butyloxycarbonyl), which resulted in the isolation of the *N*-Boc alanine derivatives **60** in excellent yields. The reduction of the *para*-nitrophenyl-substituted aziridine **24b** occurred with simulta-

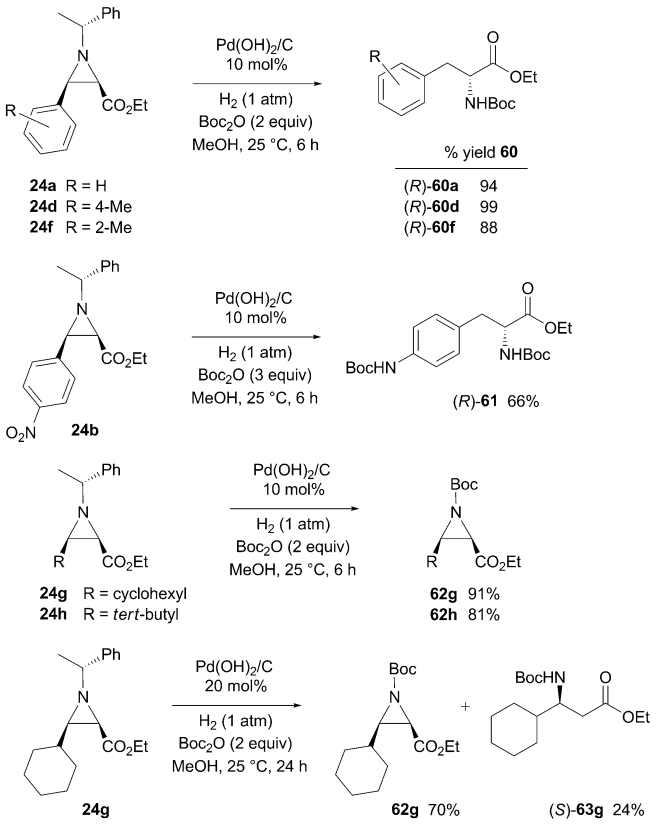
Table 7. Matched and mismatched *trans*-aziridinations of alkyl imines (*R*)-**26** with diazoacetamide **51**.[a]



	R	Ligand	Conv. [%]	**53**:**54**	Yield **53** [%][c]	Yield **54** [%][d]
1	 (*R*)-**26g**	(*S*)-VAPOL	100	>96:4	78	<3
2		(*R*)-VAPOL	100	67:33	59	30
3		(*S*)-VANOL	100	>96:4	80	<3
4		(*R*)-VANOL	100	75:25	60	20
5		$B(OPh)_3$ only	100	91:9	42[e]	4
6	 (*R*)-**26h**	(*S*)-VAPOL	87	97:3	69	2
7		(*R*)-VAPOL	70	50:50	30	30
8		(*S*)-VANOL	81	>97:3	61	<2
9		(*R*)-VANOL	63	67:33	19	10
10		$B(OPh)_3$ only	64	83:17	42[e]	8
11	 (*R*)-**26i**	(*S*)-VAPOL	100	52:48	15	14
12		(*R*)-VAPOL	100	95:5	79	4
13		(*S*)-VANOL	100	67:33	40	20
14		(*R*)-VANOL	100	95:5	80	4
15		$B(OPh)_3$ only	100	83:17	43	9

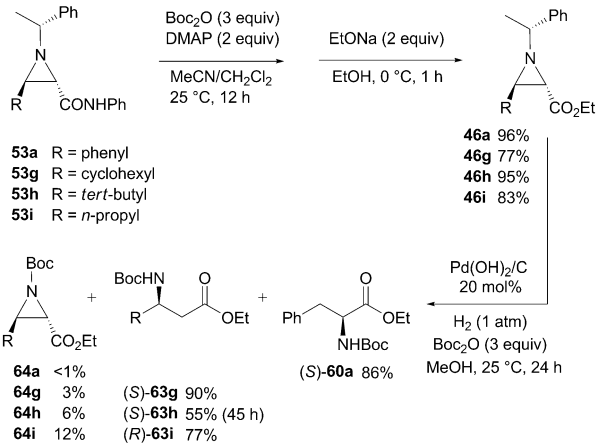
[a] Unless otherwise stated all reactions were run at 0.2 M in imine with 1.2 equivalents diazoacetamide **51** and 10 mol% catalyst in toluene at room temperature for 20–24 h. The catalyst was prepared from 1.0 equivalent of the ligand, 3.0 equivalents of $BH_3{\cdot}SMe_2$, 2.0 equivalents of PhOH and 3.0 equivalents H_2O according to Method C in the Experimental Section in the Supporting Information. All imines were oil and used without purification. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield after chromatography on silica gel. [d] Yield from ^1H NMR spectrum of the crude reaction mixture based on the isolated yield of **53**. [e] Yield from 1H NMR spectrum of the crude reaction mixture with Ph_3CH as internal standard.

neous reduction of the nitro group to an aniline and final isolation provided the bis-Boc-protected 4-aminophenylalanine derivative **61**. It was anticipated that reduction of the *para*-bromophenyl aziridine **24c** under the same conditions would lead to reduction of the bromide substituent concomitant with ring-opening based on our previous experience in the synthesis of the cell adhesion inhibitor BIRT-377.[9] In this synthesis we found that it was possible to achieve reductive ring-opening of the benzhydryl aziridine corresponding to **24c** with $BH_3{\cdot}NMe_3$ and trifluoroacetic acid with the *para*-bromide substituent being left untouched. The aliphatic-substituted *cis*-aziridines **24g** and **24h** do not undergo ring-opening under the same conditions as the aryl aziridines, but rather simply undergo reductive cleavage of the α-methylbenzyl group to yield the *N*-Boc aziridines **62g** and **62h**. If the catalyst loading and reaction time are increased, a small amount (24%) of the β-amino ester (*R*)-**63g** can be observed for the cyclohexyl aziridine **24g** (Scheme 9). This



Scheme 9.

is quite curious given that the corresponding aliphatic-substituted *trans*-aziridines **46** undergo nearly complete ring-opening under the same conditions (Scheme 10). The hydrogenation of aziridine-2-carboxylates is generally observed to be faster with aryl versus alkyl groups in the 3-position and the switch in regioselectivity with alkyl groups to opening at the 3-position to give β-amino esters has been previously observed.[10–12]



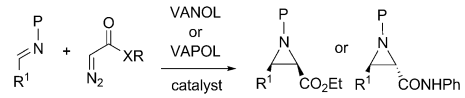
Scheme 10.

The direct reductive ring-opening of the *trans*-aziridine-2-carboxamide **53a** was relatively ineffective giving only a 40% isolated yield of the corresponding phenylalanine derivative **59a** (Scheme 8). In an effort to increase the overall efficiency of the conversion of *trans*-aziridine-2-carboxamides to α- and β-amino acid derivatives, an alternative approach was examined that begins with the initial conversion of the *trans*-aziridine-2-carboxamides **53** to the *trans*-aziridine-2-carboxylates **46** (Scheme 10). This was accomplished by the in-situ activation of the amide by the introduction of a Boc group and then nucleophilic displacement of the resulting carbamate with sodium ethoxide to generate the corresponding ethyl esters **46**. Reductive ring-opening of these *trans*-aziridine esters proceeded smoothly to give *N*-Boc protected α-amino esters **60** and the β-amino esters **63** in good to excellent yields. Note that the 3-phenylaziridine-2-carboxamide **53a** could be converted to the phenylalanine derivative **60a** in 83% overall yield, a dramatic improvement of the 40% yield for the direct reductive ring-opening (Scheme 8 vs. 10). We were quite pleased to find that unlike the *cis*-aziridine ethyl esters **24** (Scheme 9) the *trans*-aziridine ethyl esters **46** with aliphatic substituents underwent ring-opening much faster and gave good-to-excellent yields of β-amino esters. The cyclohexyl aziridine **46g** gave **63g** in 90% yield and the *n*-propyl aziridine **46i** gave **63i** in 77% yield along with a 12% yield of the unopened *N*-Boc aziridine **64i** under these conditions. The reductive ring-opening of the *tert*-butyl aziridine **46h** is slower and gives only a 55% yield of **63h** and required a doubling of the reaction time. The faster rates for the reductive ring-opening of *trans*-aziridine-2-carboxylate ethyl esters with aliphatic substituents is not understood at this time and may be a surface phenomenon of the heterogeneous catalyst involving coordination of the ester group during reduction which may be hindered by a neighboring *cis*-aliphatic substituent.

Conclusion

The catalytic asymmetric aziridination reaction catalyzed by VANOL and VAPOL boroxinate catalysts was first reported in 2000 from the reaction of ethyl diazoacetate with imines bearing a benzhydryl substituent.[1b,c] Improvements in asymmetric inductions and yields have been subsequently realized by employing other diarylmethyl substituents on the imine, such as DAM, BUDAM and MEDAM (Scheme 2). Table 8 presents the average yield and average asymmetric induction with imines derived from nine different aromatic and aliphatic aldehydes with five different *N*-substituents (including the α-methylbenzyl substituent from the present work) and with both the VANOL and VAPOL ligands. It is interesting and still quite astonishing to consider that the VANOL and VAPOL ligands give essentially the same yields and inductions in all cases. Benzhydryl amine **10** is commercially available and although it gives lower inductions, the aziridine products tend to be crystalline and often the optical purity can be increased to >99% *ee* with one crystallization.[1c] The best substituent in terms of yields and asymmetric induction is the MEDAM group and this is the substrate of choice for many applications, especially when the product aziridines are not crystalline.[4c] In the present work, it has been demonstrated that imines derived from α-methylbenzyl amine **19** will undergo the AZ reaction to give good yields of aziridines for which there is a strong matched case between the (*R*)-imine and (*S*)-VANOL- or (*S*)-VAPOL-derived catalyst for *cis*-aziridines (the matched case depends on the substituent for *trans*-aziridines). The advantage of this method is that no final enhancement of the optical purity of the aziridine products is needed and this advantage is enabled by the fact that the minor diastereomer that is formed (if any) can be easily separated. This aziridine synthesis with α-methylbenzyl amine **19** has the additional advantage that this amine is commercially available in both antipodes, each of which is about the same cost as benzhydryl amine. Furthermore, the aziridination with α-methylbenzyl amine **19** may well prove superior to those with MEDAM or BUDAM amines **12** and **13** in providing *trans*-aziridines with high optical purity.[7] Averages for *trans*-aziridines are not given for other N-substituents, since the aliphatic and aromatic imines were individually optimized for a particular N-substituent and the data for a particular N-substituent over a range imines is not yet available.[7] Thus, there are a variety of options for obtaining aziridines with high optical purity from the AZ reaction and the aziridination with α-methylbenzyl amine **19** is one that has particular features that may prove to be ideal for many situations.

Table 8. Averaged ligand and N-substituent effects over nine imines with aromatic and aliphatic substituents R^1.



N-substituents (P)[a]	Aziridine	Ligand	Average yield [%]	Average *ee* [%][b]	Source
(*R*)-α-methylbenzyl	*cis*	VAPOL	70[c,d]	100 (≥87)	this work
	cis	VANOL	72[c,e]	100 (≥90)	
	trans[f]	VAPOL	74	100 (≥90)	
	trans[f]	VANOL	75	100 (≥90)	
benzhydryl	*cis*	VAPOL	70	88	[1c]
	cis	VANOL	77	88	
DAM	*cis*	VAPOL	73	88	[4c]
	cis	VANOL	78	85	
BUDAM	*cis*	VAPOL	88	95	[4b]
	cis	VANOL	90	94	
MEDAM	*cis*	VAPOL	92	97	[4c]
	cis	VANOL	91	96	

[a] See Scheme 2. [b] % *de* is indicated in parentheses. [c] Isolated yield of purified major diastereomers. [d] Eight substrates. [e] Seven substrates. [f] Four substrates.

Experimental Section

For experimental details and characterization of the compounds please see the Supporting Information. CCDC-838600 (**37a**), 838602 (**48**), and 838601 (**53h**) contain the supplementary crystallographic data for this

paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] a) J. C. Antilla, W. D. Wulff, *J. Am. Chem. Soc.* **1999**, *121*, 5099–5100; b) J. C. Antilla, W. D. Wulff, *Angew. Chem.* **2000**, *112*, 4692–4695; *Angew. Chem. Int. Ed.* **2000**, *39*, 4518–4521; c) Y. Zhang, A. Desai, Z. Lu, G. Hu, Z. Ding, W. D. Wulff, *Chem. Eur. J.* **2008**, *14*, 3785–3803. For a review, see: d) Y. Zhang, Z. Lu, W. D. Wulff, *Synlett* **2009**, 2715–2739.

[2] For a recent review on asymmetric aziridination, see: H. Pellissier, *Tetrahedron* **2010**, *66*, 1509–1555.

[3] a) G. Hu, L. Huang, R. H. Huang, W. D. Wulff, *J. Am. Chem. Soc.* **2009**, *131*, 15615–15617; b) G. Hu, A. K. Gupta, R. H. Huang, M. Mukherjee, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 14669–14675.

[4] a) Z. Lu, Y. Zhang, W. D. Wulff, *J. Am. Chem. Soc.* **2007**, *129*, 7185–7194; b) Y. Zhang, Z. Lu, A. Desai, W. D. Wulff, *Org. Lett.* **2008**, *10*, 5429–5432; c) M. Mukherjee, A. K. Gupta, Z. Lu, Y. Zhang, W. D. Wulff, *J. Org. Chem.* **2010**, *75*, 5643.

[5] a) H.-J. Ha, K.-H. Kang, J.-M. Suh, Y.-G. Ahn, *Tetrahedron Lett.* **1996**, *37*, 7069–7070; b) K.-D. Lee, J.-M. Suh, J.-H. Park, H.-J. Ha, H. G. Choi, C. S. Park, J. W. Chang, W. K. Lee, Y. Dong, H. Yun, *Tetrahedron* **2001**, *57*, 8267–8276; c) S.-H. Lee, I.-W. Song, *Bull. Korean Chem. Soc.* **2005**, *26*, 223–224.

[6] M. Vetticatt, A. Desai, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 13104–13107.

[7] A. Desai, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 13100–13103.

[8] P. Pelagatti, M. Carcelli, F. Calbiani, C. Cassi, C. P. Elviri, U. Rizzotti, D. Rogolino, *Organmetallic* **2005**, *24*, 5836–5844.

[9] A. P. Patwardhan, V. R. Pulgam, Y. Zhang, W. D. Wulff, *Angew. Chem.* **2005**, *117*, 6325–6328; *Angew. Chem. Int. Ed.* **2005**, *44*, 6169–6172.

[10] F. A. Davis, J. Deng, Y. Zhang, R. C. Haltiwanger, *Tetrahedron* **2002**, *58*, 7135–7143, and references therein.

[11] a) D. Tanner, *Angew. Chem.* **1994**, *106*, 625; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; b) H. N. I. Osborn, J. B. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715; c) W. McCoull, F. A. Davies, *Synthesis* **2000**, 1347–1365; d) B. Zwanenburg, P. T. Holte, *Top. Curr. Chem.* **2001**, *216*, 93–124; e) J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247–258; f) P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571; g) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701–2743; h) C. Mösser, C. Bolm in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2006**; i) I. D. G. Watson, L. Yu, A. K. Yudin, *Acc. Chem. Res.* **2006**, *39*, 194–206; j) M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979–4988; k) G. S. Singh, M. D'hooghe, N. De Kimpe, *Chem. Rev.* **2007**, *107*, 2080–2135; l) C. A. Olsen, H. Franzyk, J. W. Jaroszewski, *Eur. J. Org. Chem.* **2007**, 1717–1724; m) P. Lu, *Tetrahedron* **2010**, *66*, 2549.

[12] A. P. Patwardhan, Z. Lu, V. R. Pulgam, W. D. Wulff, *Org. Lett.* **2005**, *7*, 2201–2204.

[13] a) J. M. Bao, W. D. Wulff, J. B. Dominy, M. J. Fumo, E. B. Grant, A. C. Rob, M. C. Whitcomb, S. M. Yeung, R. L. Ostrander, A. L. Rheingold, *J. Am. Chem. Soc.* **1996**, *118*, 3392–3405; b) A. Ding, W. E. G. Osminski, H. Ren, W. D. Wulff, *Org. Process Res. Dev.* **2011**, *15*, 1089–1107.

[14] R. Imwinkelried, L. S. Hegedus, *Organometallics* **1988**, *7*, 702–706.

[15] G. R. Clemo, C. Gardner, R. Raper, *J. Chem. Soc.* **1939**, 1958–1960.

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