DOI: 10.1002/ejoc.200601126

Aziridinyl Vinyl Ketones from the Asymmetric Catalytic Aziridination Reaction

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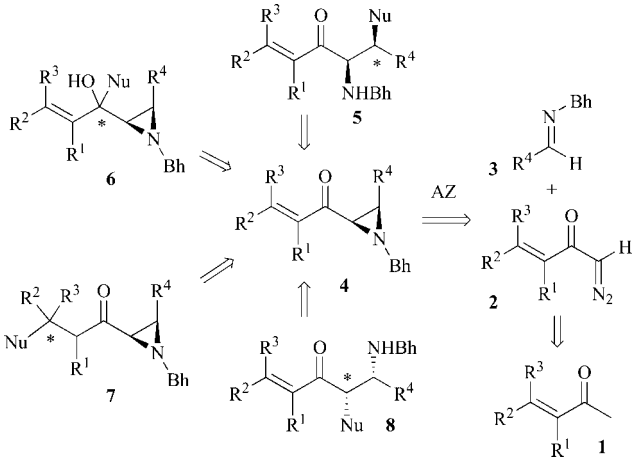
Keywords: Aziridines / Asymmetric catalysis / Lewis acids

Under the aegis of boron Lewis acids, prepared from either the vanol or vapol ligand, vinyl aziridinyl ketones can be obtained with a high degree of asymmetric induction from the catalytic asymmetric aziridination reaction (AZ) of imines and vinyl diazomethyl ketones. The products have potential as synthons for five-carbon chiral amines.

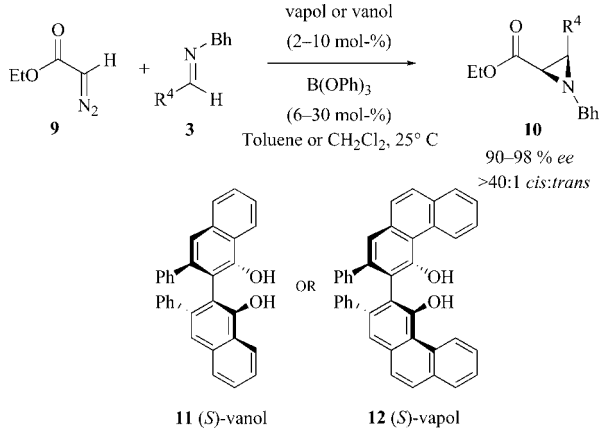
Introduction

Vinyl aziridinyl ketones of type **4** (Scheme 1) have the potential to provide a platform that could be pivotal in permitting access to a diverse array of highly functionalized five-carbon fragments. Options for the introduction of functionality into the system could be exercised at C1 and C2 by ring-opening of the aziridine, at C3 by addition to the ketone, or at C4 and C5 by 1,4-addition reactions to the alkene or by sequential Michael addition/alkylation events. Furthermore, it can be envisioned that in these processes, the stereochemical information contained in the aziridine could be transmitted to all five carbons of the vinyl aziridinyl ketone. Despite this potential, a search of the literature produced only a single report for the preparation of an acyclic 2-aziridinyl vinyl ketone.[1]



Scheme 1.

Asymmetric entry to optically pure aziridinyl vinyl ketones was envisioned from vinyl diazomethyl ketone **2** and benzhydryl imine **3** (Scheme 1) by the catalytic asymmetric aziridination reaction (AZ) that we have recently developed in our laboratories.[2,3] Catalysts prepared from either the vapol or vanol ligand and triphenylborate are capable of inducing the highly enantioselective formation of *cis*-3-substituted aziridine-2-carboxylate esters **10** from ethyl diazoacetate and benzhydryl imines (Scheme 2).[2] It was a surprise to find that the asymmetric inductions observed for this AZ reaction with both the vanol- and vapol-derived catalysts mirrored each other in a nearly perfect fashion over a range of aryl- and alkyl-substituted imines. This was not the case for aluminum catalysts employed in Diels–Alder reactions or for imino–aldol reactions where the vapol-derived catalysts were superior to those from vanol.[4,5] In contrast, vanol-derived catalysts were found to be superior to those from vapol in aluminum catalysts for the Baeyer–Villiger reaction[6] and in boron catalysts for the Diels–Alder reaction.[7]



Scheme 2.

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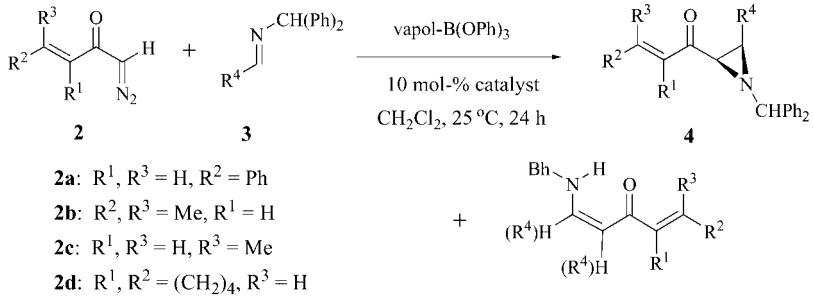
The results from the catalytic asymmetric aziridination of four different diazomethyl vinyl ketones and ten different imines are presented in Table 1. Diazomethyl vinyl ketones **2** were prepared from the corresponding methyl vinyl ketones **1** by a diazo transfer reaction following the procedure of Danheiser.[8] The imines were prepared from the corresponding aldehyde and benzhydrylamine and purified by crystallization prior to use. The catalyst was prepared by the reaction of either vanol or vapol with 3 equiv. of triphenylborate in CH_2Cl_2 heated at 55 °C for 30 min followed by the removal of the volatiles at 55 °C under high vacuum. The catalyst (10 mol-%) was then transferred to a flask containing a solution of imine in CH_2Cl_2 at room temperature, and after 5 min, 1.2 equiv. of the diazo compound was added. After 24 h, the reaction was stopped and the *cis*-aziridines were purified by silica gel chromatography and obtained as white solids. In order to ensure that the enantiomeric purity of the formed *cis*-aziridine **4** was properly measured, care was needed in its isolation; most of the *cis*-aziridines in Table 1 can be readily enhanced to greater than 99% *ee* by crystallization or simple precipitation.

Most of the reactions in Table 1 were carried out with a catalyst prepared from the vapol ligand, but in two cases the corresponding reaction with the vanol-derived catalyst was examined, and it was found that similar asymmetric inductions were observed for both ligands (Table 1, Entries 1, 2 and 18, 19). This mirrors the observation made for the asymmetric aziridination with ethyl diazoacetate for these two ligands. It was shown that ethyl diazoacetate adds to the *si* face of the imine when the aziridination reaction is performed in the presence of (*S*)-vapol and (*S*)-vanol,[2] and the same facial selectivity is assumed for the addition of

Table 1. Asymmetric aziridination of vinyl diazoketones.[a]

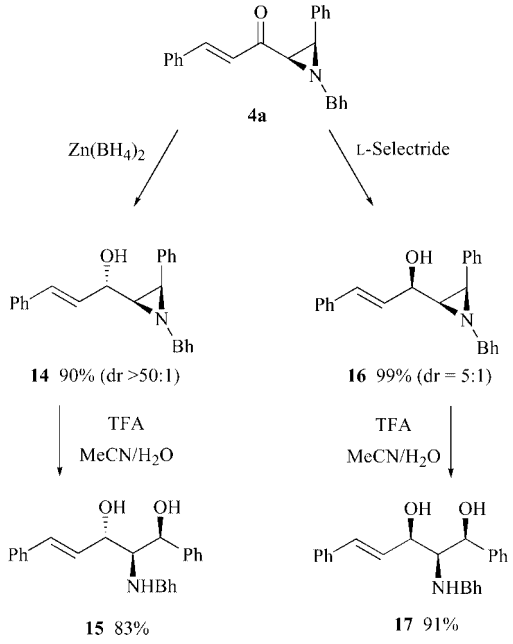


Entry	Imine	R^4	Aziridine	Yield of *cis* **4**[b] [%]	*ee* of *cis* **4**[c] [%]	*cis* **4**/*trans* **4**[d]	Yield of **13**[d] [%]
		Diazoketone **2a**					
1	**3a**	Ph	**4a**	79	95	≥50:1	15
2	**3a**	Ph	**4a**	61	92[e]	≥50:1	9
3	**3b**	2-MeC_6H_4	**4b**	45	91	≥50:1	17
4	**3c**	2-BrC_6H_4	**4c**	55	93	12:1	18
5	**3d**	2-F-5-BrC_6H_3	**4d**	64	95	14:1	12
6	**3e**	3-$NO_2C_6H_4$	**4e**	78	94	≥50:1	16
7	**3f**	4-MeC_6H_4	**4f**	71	99.7	≥50:1	17
8	**3g**	4-BrC_6H_4	**4g**	51	96	14:1	20
9	**3h**	4-$NO_2C_6H_4$	**4h**	80	95	≥50:1	8
10	**3i**	2-naphthyl	**4i**	84	98.3	≥50:1	8
11	**3j**	*c*-C_6H_{11}	**4j**	90	93	5:1	3
		Diazoketone **2b**					
12	**3a**	Ph	**4k**	76	98.1	15:1	15
13	**3f**	4-MeC_6H_4	**4l**	83	96.1	≥50:1	12
14	**3g**	4-BrC_6H_4	**4m**	76	98.5	20:1	15
15	**3h**	4-$NO_2C_6H_4$	**4n**	67	95.7	7:1	13
16	**3j**	*c*-C_6H_{11}	**4o**	75	94.4	10:1	15
		Diazoketone **2c**					
17	**3a**	Ph	**4p**	85	95.7	25:1	11
		Diazoketone **2d**					
18	**3a**	Ph	**4q**	40	82[f]	6:1	26
19	**3a**	Ph	**4q**	35	81[e]	6:1	43

[a] The catalyst was prepared from (*S*)-vapol and $B(OPh)_3$ as described in the text and the Supporting Information. All reactions were performed with imine (0.5 M) and diazo compound **2** (1.2 equiv.) in CH_2Cl_2 heated at 25 °C for 24 h. [b] Isolated yields after silica gel chromatography. [c] Measured by chiral HPLC with chromatographed *cis*-aziridine. [d] Measured by ^1H NMR spectroscopy with the crude reaction mixture. [e] This reaction was performed with a catalyst prepared from (*S*)-vanol. [f] With one batch of **2d** a 93% *ee* for **4q** was obtained.

diazomethyl vinyl ketones. With the exception of the diazo compound obtained from cyclohexenyl methyl ketone (Table 1, Entries 18 and 19), all of the reactions investigated in this work gave *cis*-aziridine **4** in greater than 90% *ee*. This includes aziridines derived from alkyl imines and aryl imines that have both electron-withdrawing and electron-donating groups in the *para*, *meta*, and *ortho* positions. The yields of the *cis*-aziridines are generally good to excellent, except for diazo methyl ketone **2d**, which gave nearly equal amounts of enamine product **5**. This vinyl diazo methyl ketone is the only one examined that has a substituent on the vinyl group alpha to the ketone. The *cis* to *trans* selectivity is generally good to excellent and does vary a bit but does not seem to correlate with the electron density on the aryl ring or the position of the substituent on the aryl ring.

As an initial foray into a study aimed at the development of aziridinyl vinyl ketones **4** as synthons for the asymmetric synthesis of five-carbon amine fragments, we examined the diastereoselectivity of the reduction of the ketone unit in vinyl diazomethyl ketone **4a** (Scheme 3). The reduction of aziridinyl ketones is known to be highly stereoselective under chelation-controlled conditions with bidentate Lewis acids.[9] Thus, the reduction of **4a** was first examined with zinc borohydride. Despite our concerns with the presence of the large benzhydryl substituent on the nitrogen which might prevent coordination of zinc, it proved possible to reduce the ketone moiety in **4a** with zinc borohydride with >50:1 selectivity for diastereomer **14**, which would be the resulting product from a chelation-controlled reduction.[10] Nonchelation-controlled reduction of the ketone functionality in **4a** could be effected with L-Selectride in 99% yield and with a 5:1 selectivity for diastereomer **16**, which could be readily separated from **14**. Hydrolytic opening of the aziridine ring in both **14** and **16** could be achieved in high yield and with complete inversion at the C3 position to give *syn*,*anti*-aminodiol **15** and *syn*,*syn*-aminodiol **17**, respectively.



Scheme 3.

In conclusion, we have shown that the asymmetric catalytic aziridination reaction (AZ) can be extended to diazomethyl vinyl ketones with high degrees of asymmetric induction. The aziridinyl vinyl ketone products can be readily and stereoselectively transformed into chiral five-carbon amine units. The further development of aziridinyl vinyl ketones as synthons for polyfunctionalized amines will be reported in due course.

Experimental Section

(*S*)-vapol (27 mg, 0.05 mmol) in dry dichloromethane (1 mL) was added to a flame-dried 25-mL single-necked round-bottomed flask which had the 14/20 joint replaced with a threaded high-vacuum telfon stopcock. After the addition of triphenylborate (43.5 mg, 0.15 mmol), the stopcock was sealed, and the flask was heated at 55 °C for 1 h, and then a high vacuum was applied for 30 min with the temperature maintained at 55 °C. The catalyst was then dissolved in dichloromethane (0.5 mL) and transferred by syringe to a 25-mL flame-dried flask, which had been previously charged with the requisite imine (0.50 mmol) in dichloromethane (0.5 mL). After stirring for 10 min, the desired vinyl diazomethyl ketone **2** (0.6 mmol) was added. The reaction was monitored by TLC and was found to be complete after 24 h at 25 °C. The reaction mixture was diluted with dichloromethane (5 mL) and then saturated aqueous sodium hydrogencarbonate (5 mL) was added. The organic layer was separated and then washed with brine (3 mL), dried with magnesium sulfate, filtered, and concentrated under vacuum to give the crude product. The *cis*/*trans* ratio of aziridine **4** was determined by the relative integration of the ^{1}H NMR spectroscopic signals for the methine protons on the three-membered ring in the spectrum of the crude reaction mixture. For most aziridines, these protons appear as doublets between δ = 2 and 4 ppm and have coupling constants of 7 Hz for the *cis*-aziridines and ca. 2 Hz for the *trans*-aziridines. Purification by flash chromatography on silica gel (hexanes/ethyl acetate) gave the pure *cis*-aziridines as white solids. The asymmetric induction was measured by chiral HPLC on the purified *cis*-aziridines. Care is required in the accurate determination of the induction because the pure enantiomers of **4** are less soluble than the racemate. The amount of enamine side product was calculated from the isolated yield of the *cis*-aziridine and the relative integration of the NH signal of the enamine and the three-membered ring methine proton of the *cis*-aziridine in the crude reaction mixture. The enamine side product is often formed as a mixture of isomers and the NH absorption for both generally appear between δ = 11.5 and 12.5 ppm. For each different substrate, a sample of the racemic aziridine was prepared by the reaction of the appropriate imine and vinyl diazomethyl ketone catalyzed by boron trifluoride etherate. The racemic aziridine was utilized in the determination of the retention time of each enantiomer in the chiral HPLC analysis. The absolute configuration of the *cis*-aziridine product was assumed to result from *si* face addition to the imine by the catalyst derived from (*S*)-vapol as was shown to be the case for the reaction with ethyl diazoacetate.[2] Aziridine **4a**: 79% yield, 95% *ee*, *cis*/*trans* ≥50:1, $[\alpha]_D^{20}$ = +109.2 (*c* = 1, CH_2Cl_2). White solid, m.p. 150 °C, R_f = 0.33 (hexanes/ethyl acetate, 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (d, *J* = 7.1 Hz, 1 H), 3.38 (d, *J* = 7.1 Hz, 1 H), 3.99 (s, 1 H), 6.81 (d, *J* = 16.2 Hz, 1 H), 7.08–7.41 (m, 17 H), 7.51–7.55 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.8, 52.4, 78.3, 123.6, 127.2, 127.3, 127.4, 127.5, 127.60, 127.63, 128.0, 128.3,

128.6, 128.7, 130.3, 134.6, 135.1, 142.2, 142.3, 142.5, 194.8 (one sp^2 C not located) ppm. IR (KBr): $\tilde{\nu}$ = 3062, 3029, 1683, 1657, 1610, 1494, 1452, 1206, 1099, 764 cm^{-1}. MS (EI): *m*/*z* (%) = 415 (1) $[M]^+$, 248 (77), 167 (100), 131 (40), 115 (42), 103 (34). $C_{30}H_{25}NO$ (415.5): calcd. C 86.71, H 6.06, N 3.37; found C 86.44, H 5.97, N 3.38. HPLC (chiralcel OD, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL min^{-1}): t_R = 8.0 min (major enantiomer), t_R = 11.2 min (minor enantiomer).

Supporting Information (see footnote on the first page of this article): Procedures for the preparation and catalytic asymmetric aziridination of ketones **4**, including spectroscopic data. Procedure for the reduction of **4a** with L-Selectride or with zinc borohydride. Formation of derivative **18**, procedure for the ring-opening reaction of the aziridines with aqueous trifluoroacetic acid, and preparation of derivative **19**.

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[10] The relative stereochemistry of **14** was determined by X-ray diffraction analysis on its *para*-nitrobenzoyl derivative, see Supporting Information.

Received: December 26, 2006
Published Online: March 14, 2007

