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A Stereospecific Synthesis of Vicinal Amino Alcohols by Aminolysis of Vinylepoxides

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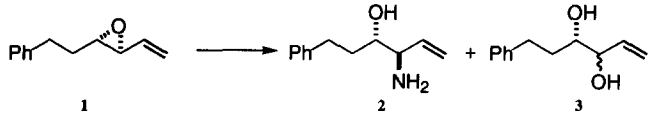
Abstract: Several vinylepoxides have been prepared and subjected to a TsOH·H_2O-catalyzed aminolysis reaction to afford the corresponding amino alcohols in good yields. The nucleophilic addition is stereospecific and proceeds with high regioselectivity at the allylic position, unless other stereoelectronic effects competes. The aminolysis reaction is sensitive to steric hindrance at or in the proximity of the oxirane nuclei. © 1997 Elsevier Science Ltd. All rights reserved.

Acyclic scalemic *vic*-amino alcohols are important intermediates in natural product synthesis and, more recently, as precursors for various chiral auxiliaries and catalysts for asymmetric synthesis. As a consequence, the development of efficient routes towards these compounds, especially those congeners that are not readily available from amino acids, has been the focus of recent reports. In this respect several conceptually different strategies have been employed for the preparation of *vic*-amino alcohols: (1) elaboration of an acyclic substrate in which the required stereogenic centers are already present, e.g. ring-opening of epoxides,[1a] aziridines[1b] and cyclic sulfates[1c] by suitable nucleophiles as well as manipulations of ene diols,[1d] (2) stereoselective addition reactions to α-amino aldehydes and ketones[1e] and addition of chiral 3-amino allylboranes to aldehydes,[1f] (3) nucleophilic addition to imines[1g] and (4) aminohydroxylation of olefins.[1h] Although aminolysis of epoxides is conceivably an attractive entry to amino alcohols this reaction is usually hampered by its poor regioselectivity, except for terminal oxiranes.[2] In contrast, we have investigated the ring-opening of vinylepoxides with ammonia and amines and found that the reaction is stereospecific and highly regioselective, affording the corresponding 2-vinyl-2-amino alcohols, and herein we detail our results.

The vinylepoxides[3] used in this study were prepared from the corresponding Sharpless epoxy alcohols by Swern oxidation followed by Wittig olefination. Since it has previously been noted that the intramolecular acid-catalyzed opening of vinylepoxides by oxygen nucleophiles is controlled by stereoelectronic effects, proceeding by a regioselective and stereospecific attack at the allylic oxirane carbon,[4] our initial focus was directed towards defining reaction conditions that would result in similar selectivities with nitrogen nucleophiles (Table 1). Attempts to effect the aminolysis of vinylepoxide **1** by subjecting it to ammonium hydroxide resulted in a slow reaction,[5] affording amino alcohol **2** in low yield along with recovered starting material (entry 1). Gratifyingly, however, **2** was the only detectable isomer which seems to indicate that this ring-opening is controlled by the same preferences as discussed above. Repeating the experiment in NH_3 using water (2 eq) for the in situ formation of NH_4OH gave once again **2** in low yield together with diols **3** (entry 2). It is interesting to note that **3** are formed as a mixture of diastereomers, indicating that their mode of

formation might differ from that of amino alcohol **2**, and that no traces of the product derived from a S_N2'-attack on **1** could be detected in the crude reaction mixtures. In an effort to suppress the formation of **3** a catalytic amount of anhydrous TsOH was added to the reaction mixture which, somewhat surprisingly, completely retarded the desired reaction (entry 3). Finally, it was found that TsOH·H_2O in NH_3 smoothly catalyzed the aminolysis, affording amino alcohol **2** in 77% yield along with only minor amounts of diols **3** (entry 4).

Table 1. Aminolysis of Vinylepoxide 1.



1 2 3

		Yield (%)[a]	
Entry	Conditions	**2**	**3**
1	NH_4OH, rt→Δ, 10 d	13	0
2	NH_3, H_2O (2 eq), 80 °C, 3 d	11	62
3	NH_3, TsOH (0.05 eq), 80 °C, 3 d	0	0
4	NH_3, TsOH·H_2O (0.05 eq), 80 °C, 3 d	77	10

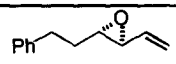
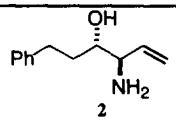
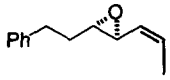
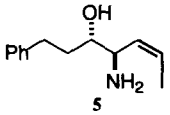
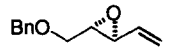
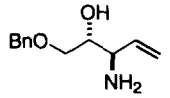
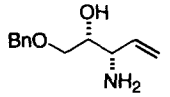
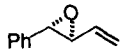
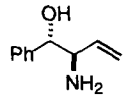
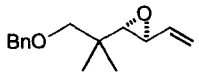
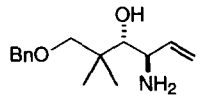
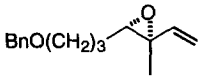
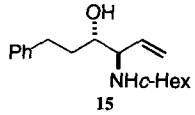
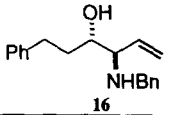
[a] In all cases unreacted **1** could be recovered after the reaction.

The results of some typical aminolysis experiments which defines the scope of the present method are collected in Table 2. As can be seen, 2,3-disubstituted oxiranes are the best substrates in this reaction (entries 1-4) with the *trans*-derivatives affording *anti*-amino alcohols while a *cis*-epoxide is transformed into the corresponding *syn*-derivative (entries 3,4) in high yields, thus allowing for a nice entry to both series of derivatives. In contrast to the Pd-catalyzed transformation of ene diols into oxazolidin-2-ones, and hence to amino alcohols, for which it has been shown that the stereochemical integrity of the alkene moiety is not preserved,[1d] the aminolysis of vinylepoxides proceeds without such erosion of the olefin geometry (entry 2). However, aminolysis of **10** gives a 4:1 mixture of **11** and the regioisomeric amino alcohol in 70% combined yield, indicating a subtle stereoelectronic balance between the allyl and benzylic positions (entry 5). To probe the influence of a phenyl group in these ring-openings *trans*-2-phenyl-3-methyloxirane was subjected to the standard reaction conditions affording, somewhat surprisingly, a 1.7:1 mixture of 2-amino-1-phenylpropanol and its regioisomer, each as a single stereoisomer, and we have at present no satisfying explanation for this result. When using sterically hindered substrates, such as **12** and **14** (entries 6, 7), the aminolysis becomes very slow or is completely inhibited, although the unreacted starting material can be recovered in each case. Finally, the influence on the reaction outcome when using primary amines as nucleophiles, exemplified with cyclohexyl- and benzylamine (entries 8, 9), has been examined and shown to afford the expected products in good yield.

The stereochemistry of the amino alcohols discussed above were, in each case, confirmed by conversion into the corresponding vinylaziridine (Ph_3P, DEAD) or oxazolidinone ($(Cl_3CCO)_2O$, $^iPr_2NEt$) followed by measuring the relevant coupling constants in their ^1H NMR spectra. The *trans*-vinylaziridines derived from *anti*-amino alcohols showed J=2.3-2.6 Hz and the *cis*-3,4-disubstituted oxazolidinones prepared

from the same precursors had J=8.0-8.1 Hz, while for the *cis*-aziridine prepared from **9** it was J=6.2 Hz, which is in accord with the assigned structures.[1f, 6] It should be noted that the present route allows for an efficient and flexible entry to various vinylaziridines, compounds that are of current interest in natural product synthesis as well as precursors for peptidomimetics, and the results from such applications will be the focus of forthcoming reports.

Table 2. Aminolysis of Various Vinylepoxides.[a]

Entry	Substrate	Amine	Product	Yield (%)[b]
1	 **1**	NH_3	 **2**	77
2	 **4**	NH_3	 **5**	69
3	 **6**	NH_3	 **7**	93
4	 **8**	NH_3	 **9**	80
5	 **10**	NH_3	 **11**	56[c]
6	 **12**	NH_3	 **13**	23[d]
7	 **14**	NH_3	-	-[e]
8	**1**	*c*-HexNH_2	 **15**	82
9	**1**	$BnNH_2$	 **16**	78[f]

[a] All reactions were carried out in neat ammonia or amine with $TsOH{\cdot}H_2O$ (0.05 eq) at 130 °C for 3 days (except entry 1: 80 °C). The reaction conditions has not been optimized for each individual substrate. [b] Isolated yields. [c] 14% of the regioisomeric amino alcohol was isolated. [d] 72% recovered **12**. [e] No reaction, **14** was recovered. [f] A small amount (<5%) of the regioisomeric amino alcohol was isolated.

General procedure for the aminolysis of vinylepoxides: Freshly distilled (Na) ammonia (8 ml) is condensed, under an inert atmosphere, into a glass tube containing the vinylepoxide (1.35 mmol) and $TsOH \cdot H_2O$ (0.05 eq). The tube is placed in a metal cylinder which is then sealed and heated to 130 °C for 3 days. The cylinder is then cooled to rt, the ammonia is allowed to evaporate and the residue is diluted with Et_2O. Standard work up and flash chromatography then gives the corresponding amino alcohol.

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1. For some representative examples, see: (a) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Ibuka, T.; Nakai, K.; Akaji, M.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron* **1996**, *52*, 11739. Hwang, G.-I.; Chung, J.-H.; Lee, W. K. *J. Org. Chem.* **1996**, *61*, 6183. Takeuchi, H.; Koyama, K. *J. Chem. Soc. Perkin Trans. 2* **1981**, 121. (c) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623. (d) Xu, D.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 951. (e) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531. (f) Barrett, A. G.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677. (g) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785. Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 6766. Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469. (h) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451.
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