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Regio- and Stereoselective Ring-opening Reaction of 2,3-Epoxy Amines with Organo-aluminum Reagents Leading to 2-Substituted 3-Amino Alcohols

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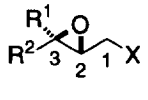
Abstract: Alkylation, alkynylation, and hydride reduction occurred regioselectively at the C-2 position of 2,3-epoxy amines with retention of the configuration at the C-2 upon treatment with organo-aluminum reagents to give 2-substituted 3-amino alcohols. The reactions are considered to proceed via aziridinium ion intermediates. Copyright © 1996 Elsevier Science Ltd

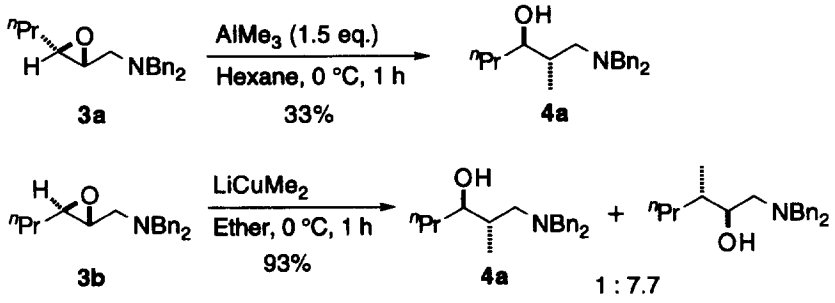
The Katsuki-Sharpless asymmetric epoxidation is one of the most useful asymmetric reactions easily available to synthetic chemists.[1] Development of the regio- and stereoselective ring-opening reactions of optically active 2,3-epoxy alcohols (**1**), obtained by the Katsuki-Sharpless asymmetric epoxidation, has enabled these compounds to serve as extremely useful synthetic intermediates.[2] Recently, the chemistry of 2,3-epoxy derivatives, where the hydroxy oxygen atom of an 2,3-epoxy alcohol is replaced by a different heteroatom, such as sulfur (**2**) and nitrogen (**3**), has aroused the interest of organic chemists, since the new systems represent new, optically active building-blocks with a high degree of functionality, possessing considerable potential for synthetic manipulation.[3] In a previous paper we reported the highly regio- and stereoselective ring-opening reaction of 2,3-epoxy sulfides (**2**) with organo-aluminum reagents, which was considered to proceed via episulfonium ion intermediates, to give C-2 substituted products with complete retention of the configuration at the C-2, or sulfenyl-shifted C-1 substituted products with complete inversion of the configuration at the C-2.[4] Here we wish to report the regio- and stereoselective ring-opening reaction of 1-dibenzylamino-2,3-epoxyalkanes (**3**) with organo-aluminum reagents, giving 2-substituted 3-amino alcohols.



1 X = OH
2 X = SR^3
3 X = NR^3_2

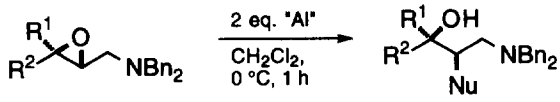
When 2,3-epoxy amine **3a** was treated with 1.5 equimolar amount of trimethylaluminum in hexane at 0 °C for 1 h, C-2 methylated **4a** was obtained in 33% yield with retention of the configuration at the C-2, and neither a diastereo- nor regio-isomer was detected; the major by-product was the hydrolyzed product, and 28% of the starting material **3a** was recovered (Scheme 1). The structure of the methylated product **4a** was identical with that of the minor regio-isomer in the products of the reaction of **3b** with Me_2CuLi (Scheme 1). Thus, the present reaction was confirmed to give the anti product on the basis of the fact that the ring-opening reaction of *trans*-epoxides via metal-chelating intermediates usually affords anti products exclusively.

Scheme 1



Brief optimization of the conditions for the reaction of **3a** with trimethylaluminum showed that 2 equimolar amounts of the organo-aluminum reagent were required in order to complete the reaction and to obtain the ring-opened product in high yield. A nonpolar solvent such as dichloromethane gave the best result, whereas in ether the reaction did not take place. Thus, we carried out the reaction of 2,3-epoxy amines **3** with organo-aluminum reagents under the optimized conditions. The results are listed in Table 1.[5]

Table 1. The Reaction of 2,3-Epoxy Amines with Various Organo-aluminum Reagents[a]



3a–c **4a–i**

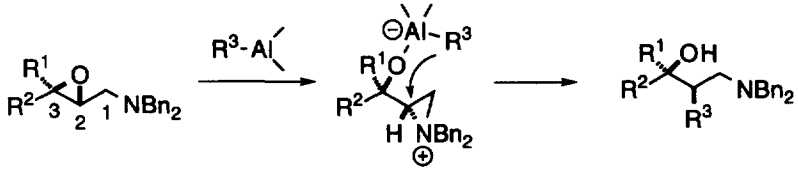
Entry	Substrate	R^1	R^2	"Al"	Product	Yield/%[b]
1	**3a**	^{n}Pr	H	$AlMe_3$	**4a**	81
2				$AlEt_3$	**4b**	73
					4f	7
3				$Et_2AlC{\equiv}CPh$	**4c**	91
4	**3b**	H	^{n}Pr	$AlMe_3$	**4d**	92
5				$AlEt_3$	**4e**	75
					4f	15
6				DIBAL	**4f**	91
7				$Et_2AlC{\equiv}CPh$	**4g**	92
8	**3c**	H	^{i}Pr	$AlMe_3$	**4h**	87
9				DIBAL	**4i**	86

[a] The reaction was carried out in dichloromethane at 0 °C, and 2 equimolar amounts of the organo-aluminum reagent were employed. [b] Isolated yield.

As can be seen from Table 1, the reaction occurred regioselectively at the C-2 with retention of the configuration at the C-2 and gave the corresponding ring-opened product in excellent yield in each case. The reaction has the following features: (1) The stereochemistry of the epoxides does not affect the regioselectivity of the reaction (Entries 1 and 4). (2) The kind of nucleophilic group attached to the aluminum atom exerts no effect on the regio- and stereoselectivities of the reaction (Entries 4–7). Although in the reaction with triethylaluminum, a minor product **4f**, formed by a hydride attack at the C-2, was obtained, the regioselectivity was maintained; the ring-opening reaction occurred exclusively at the C-2 (Entries 2 and 5). (3) An alkyl group at the α-position to the oxirane has no effect on the regio- and stereoselectivities of the reaction (Entries 8–9).

Taking into account the exclusive C-2 regioselectivity and the complete retention of the stereochemistry at the C-2, the present reaction is likely to proceed via an aziridinium ion intermediate (Scheme 2). The organoaluminum reagent coordinates to the epoxide oxygen, and the nitrogen atom attacks at the C-2 from the back-side of the C–O bond with the scission of the C–O bond, forming the fairly stable aziridinium ion **5**. Then, an intramolecular nucleophilic attack of the R^3 group occurs at the C-2 of aziridinium ion **5** from the back-side of the C–N bond to give C-2 ring-opened product **4** with retention of the configuration.[6]

Scheme 2



3 **5** **4**

A typical procedure is as follows: To a stirred mixture of 1.2 ml of 1.0 M trimethylaluminum (hexane solution, 1.2 mmol) and dichloromethane (2 ml) was added *cis*-1-dibenzylamino-2,3-epoxyhexane (**3a**, 178.2 mg, 0.6 mmol) in dichloromethane (2 ml) at 0 °C, and stirring was continued for 1 h. Then, the reaction mixture was diluted with ethyl acetate (5 ml) and treated successively with NaF (1 g, 24 mmol) and water (0.13 ml, 7 mmol). Vigorous stirring of the resulting suspension was continued at room temperature for 30 min. The mixture was filtered through a pad of anhydrous Na_2SO_4, and the remaining solid was washed with ethyl acetate (3×5 ml). The combined filtrate and washings were concentrated with a rotary evaporator, giving the crude ring-opened product. Purification by preparative TLC (eluent: AcOEt/hexane = 1/4) gave 151.6 mg of pure 3-amino alcohol **4a** (81% yield) as a colorless oil.

In conclusion, we were able to successfully control the regio- and stereoselectivities of the ring-opening reaction of epoxides by using the neighboring group participation of an amino group. Since 2,3-epoxy amines are readily available from 2,3-epoxy alcohols and since exclusive regio- and stereoselectivities have been achieved, the present reaction, coupled with the Katsuki-Sharpless asymmetric epoxidation, would be applicable to the synthesis of optically active 2-substituted 3-amino alcohols, which exist in several classes of natural products and show interesting pharmacological properties.[7] Further investigation of the synthetic application of this reaction is now in progress.

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5. Satisfactory ^{1}H NMR and IR spectra were obtained for all of the products listed in Table 1.
6. The argument for the intramolecular nucleophilic attack is based on Rayner's finding that an intermolecular nucleophilic attack to an aziridinium ion occurred preferentially at the C-1 (see ref. 3d).
7. See, for example, a) Glasby, J.S. *Encyclopaedia of Antibiotics, 2nd Edn,* Wiley: New York, 1979.
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