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Totally Selective Ring-Opening of Amino Epoxides with Ketones: A General Entry to Enantiopure (2*R*,3*S*)- and (2*S*,3*S*)-3-Aminoalkano-1,2-diols

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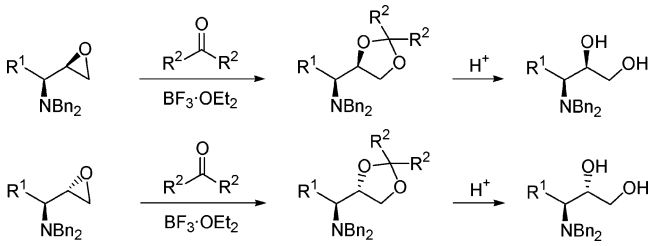
ABSTRACT



Transformation of enantiopure diastereoisomers (2*R*,1′*S*)- and (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides into the corresponding 4-(1-aminoalkyl)-1,3-dioxolanes is achieved by reaction with different ketones in the presence of BF_3·Et_2O. The conversion takes place in very high yields, total selectivity, and without epimerization. A mechanism to explain this transformation is proposed. The obtained 1,3-dioxolanes can be deprotected, and (2*R*,3*S*)- and (2*S*,3*S*)-3-aminoalkano-1,2-diols were isolated.

The direct transformation of epoxides into 1,3-dioxolanes has been previously reported using several Lewis acid catalysts such as BF_3·OEt_2,[1] $SnCl_4$,[2] $SnCl_2$,[3] and $TiCl_4$[4] and other catalysts.[5] However, in some of these methodologies, poor selectivity or yields were obtained. In addition, the synthesis of 1,3-dioxolanes derived from other acyclic ketones different from propanone was unsuccessful,[1,3] and only one paper describing the reaction of an optically pure epoxide with propanone without racemization has been described.[6] Given these facts, a general methodology to transform enantiopure epoxides into 1,3-dioxolanes without racemization and by using different acyclic ketones would be desirable.

In addition, the enantiopure 3-aminoalkano-1,2-diols obtained by deprotection of the synthesized 4-(1-aminoalkyl)-1,3-dioxolanes are important building blocks.

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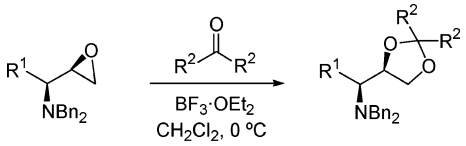
Previously, we have also described an efficient synthesis of enantiopure (2*R*,1′*S*)- or (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides, by total stereoselective reduction of the easily available α-amino-α′-chloroketones[7] with $LiAlH_4$ or by highly stereoselective addition of in situ generated iodomethyllithium (from diiodomethane and methyllithium) to α-aminoaldehydes, respectively.[8]

Building on these results, we now report the conversion of both enantiopure diastereoisomers (2*R*,1′*S*)- and (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides into the corresponding 4-(1-aminoalkyl)-1,3-dioxolanes without epimerization, by reaction with different ketones in the presence of $BF_3{\cdot}OEt_2$. The obtained 1,3-dioxolanes were deprotected, and enantiopure (2*R*,3*S*)- and (2*S*,3*S*)-3-aminoalkano-1,2-diols were isolated in high yield with total or high diastereoselectivity.

Initial attempts involved the reaction of (2*R*,1′*S*)-2-(1-aminoalkyl)epoxides with propanone, in the presence of $BF_3{\cdot}Et_2O$ at 0 °C, for 1 h, with propanone also being used as the solvent. Hydrolysis of the reaction mixture gave enantiopure (4*R*,1′*S*)-4-(1-aminoalkyl)-2,2-dimethyl-1,3-dioxacyclopentanes **2** in very high yields (>89%) as the sole product (Scheme 1, Table 1).

Scheme 1. Synthesis of 1,3-Dioxolanes **2**



1 **2**

Table 1. Synthesis of 1,3-Dioxolanes **2**

entry	**2**	R^1	R^2	yield(%)[a]
1	**2a**	Me	Me	90
2	**2b**	Me	Et	86
3	**2c**	Me	$(CH_2)_4$	92
4	**2d**	*i*-Bu	Me	89
5	**2e**	*i*-Bu	$(CH_2)_5$	87
6	**2f**	Bn	Me	92

[a] Isolated yield after column chromatography based on the starting amino epoxide **1**.

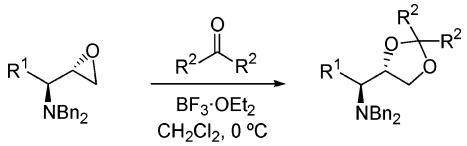
Attempts to obtain 1,3-dioxolanes derived from other ketones (cyclohexanone, cyclopentanone, pentan-3-one) were also successful, in contrast to previous results.[3] In these cases, the reaction were carried out with 1.1 equiv of ketone, CH_2Cl_2 was used as solvent at 0 °C for 1 h, and no important differences were observed, giving the corresponding 1,3-dioxolanes **2** in very high isolated yields.[9]

The selectivity of the reaction was determined by ^1H NMR spectroscopy (300 MHz) of the crude mixture of products, showing the presence of a single diastereoisomer. After analyses of NMR data we have concluded that the reaction takes place with total regioselectivity and without epimerization, in contrast to other previously described methods.

The structure of compounds **2** and, consequently, the absolute configuration was established by single-crystal X-ray analysis of **2d**.[10]

To investigate the scope of this reaction, we have subjected the other diastereoisomers, (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides **3**, to the same reaction conditions (ketones and $BF_3{\cdot}Et_2O$, 0 °C, 1 h). In all cases, the corresponding (4*S*,1′*S*)-4-(1-aminoalkyl)-1,3-dioxolanes **4** (Scheme 2 and Table 2) were obtained in high or excellent yields (> 83%).

Scheme 2. Synthesis of 1,3-Dioxolanes **4**



3 **4**

Table 2. Synthesis of 1,3-Dioxolanes **4**

entry	**4**	R^1	R^2	de (%)[a]	yield(%)[b]
1	**4a**	Me	Me	>98	95
2	**4b**	*i*-Bu	Et	91	83
3	**4c**	*i*-Bu	$(CH_2)_5$	91	85
4	**4d**	Bn	Me	92	91
5	**4d**	Bn	Me	80[c]	86
6	**4e**	Bn	Et	92[d]	84
7	**4f**	Bn	$(CH_2)_4$	>98[d]	83

[a] Diastereoisomeric excess determinated by ^1H NMR analysis of the crude products. [b] Isolated yield after column chromatography based on the starting amino epoxide **3**. [c] The epoxide was prepared from $LiCH_2Cl$ (de = 80%); see ref 7. [d] Diastereoisomeric excess determinated by GC−MS analysis of pure products.

The synthesis of dioxolanes **4** with the same diastereoisomeric excess (de) as the starting amino epoxides **3**[11] was

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(9) **Representative Experimental Procedure.** To a stirred solution of the corresponding amino epoxide **1** or **3** (0.2 mmol) in CH_2Cl_2 (1 mL, or propanone when this ketone was used), $BF_3{\cdot}OEt_2$ (0.025 mL, 0.2 mmol) and the corresponding ketone (0.22 mmol) were added at 0 °C. After 1 h of stirring, an aqueous saturated solution of sodium bicarbonate (5 mL) was added, and the mixture was stirred at room temperature for 5 min. Then, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (hexane/EtOAc 20:1) provided pure compounds **2** and **4**.

(10) CCDC-252205 (**2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or the Cambridge Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44)1223-336.033; or deposit@ccdc.cam.ac.uk).

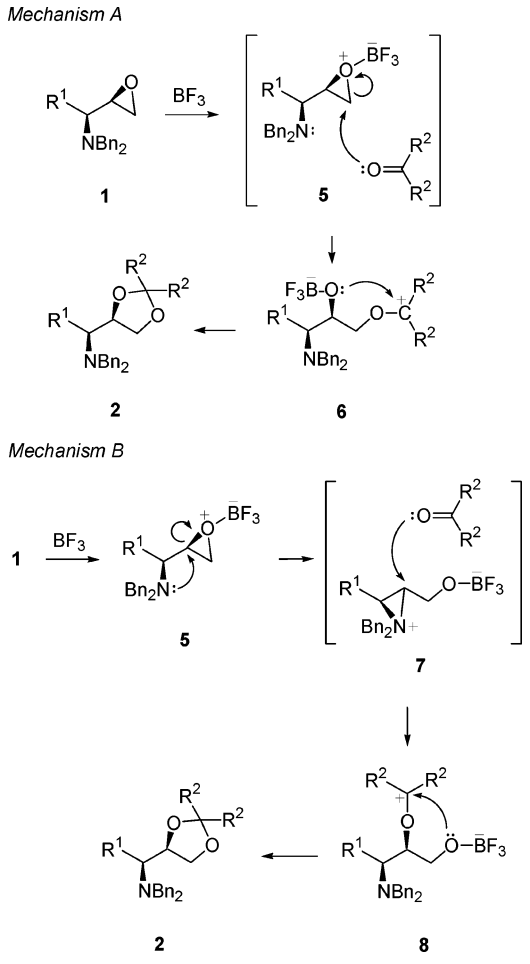
(11) (1′*S*,4*S*)-2-(1-aminoalkyl)epoxides **3** were obtained with a diastereoselection ranging from 91% to >98%; see ref 7.

an indirect support of the total selectivity of the ring-opening reaction. The de was determined by ^{1}H NMR (300 MHz) of the crude mixture of products or by GC−MS of pure compound.

As is shown in Tables 1 and 2, transformation of amino epoxides **1** and **3** into 1,3-dioxolanes **2** and **4** seems to be general. Therefore, the reaction was performed with both diastereisomers of amino epoxides derived from alanine, leucine, and phenylalanine[7] and several ketones (linear and cyclic). Furthermore, in contrast to previous results,[3] it is noteworthy that the reaction of aminoepoxides with ketones can be carried out without epimerization and by using ketones other than propanone.

This transformation and the observed stereochemistry of the products **2** and **4** may be explained by assuming the selective complexation of the epoxide oxygen with the Lewis acid, followed by nucleophilic C-3 opening of the epoxide by the carbonyl oxygen of ketone through a S_N2-like mechanism (mechanism A, Scheme 3) and finally dioxolane

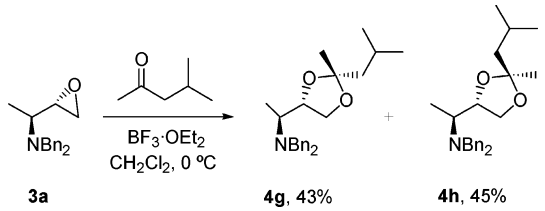
Scheme 3. Proposed Mechanism



ring formation. Alternatively, after coordination of the oxirane oxygen to the BF_3, an intramolecular ring opening at C-2 by the dibenzylamino group, with inversion of configuration, would afford the aziridinium salt **7**. Ketones would react with the aziridinium intermediate **7** (mechanism B) to afford the same final compound **2**.

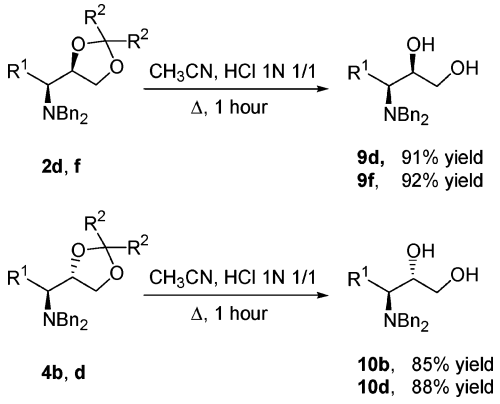
When the reaction was carried out with unsymmetrical ketones, a mixture of diastereoisomers (approximately 1:1) was obtained. Interestingly, the two obtained diastereoisomers could be separated by conventional column chromatography. The stereochemistry of both diastereoisomers was unambiguosly assigned by NOESY experiments.

Scheme 4. Reaction with No Symmetrical Ketone



The 1,3-dioxolanes **2** and **4** can be easily deprotected by acid treatment to provide enantiopure (2*R*,3*S*)- or (2*S*,3*S*)-3-aminoalkano-1,2-diols **9** or **10** in very high yield. Hence, the treatment of aminoepoxides **1** and **3** with ketones and subsequent deprotection allows access to the same two diastereoisomers, which could be obtained by a hypothetical hydroxymethylenation of α-aminoaldehydes following both nonchelation and chelation control mechanism.

Scheme 5. Deprotection of 1,3-Dioxolanes



In conclusion we have described an efficient transformation of (2*R*,1′*S*)- and (2*S*,1′*S*)-2-(1-aminoalkyl)epoxides into the corresponding 4-(1-aminoalkyl)-1,3-dioxolanes by reaction with different ketones in the presence of BF_3·OEt_2. The reaction takes place with very high yield (82−95%) and without epimerization. The obtained 1,3-dioxolanes were deprotected and enantiopure (2*R*,3*S*)- or (2*S*,3*S*)-3-aminoalkano-1,2-diols were isolated in very high yield with total or very high stereoselectivity.

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Supporting Information Available: General methods; spectroscopic data of **2**, **4**, **9**, and **10**; and ^{13}C NMR spectra of **2**, **4**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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