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Synthesis of enantiopure 2-amino-1-phenyl and 2-amino-2-phenyl ethanols using enantioselective enzymatic epoxidation and regio- and diastereoselective chemical aminolysis

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Abstract—Several enantiopure 1,2-amino alcohols have been prepared by combining a stereoselective enzymatic epoxidation of styrenes with regio- and stereoselective chemical reactions. An interesting reactivity has been noted concerning the reaction of epoxides and NH_3 under microwave activation.

1. Introduction

The 1,2-amino alcohol motif is present in a number of bioactive natural products[1] (such as alkaloids,[2a–c] amino sugars,[2d] enzyme inhibitors,[2e,3a–c] and antibiotics[3d,e]). In addition, they are frequently employed in asymmetric synthesis as chiral auxiliaries or chiral catalysts.[4] As a consequence, synthetic chemists continue to develop new methods for their efficient asymmetric synthesis.

Enantiopure 1,2-amino alcohols are readily accessible if they can be derived from proteinogenic amino acids. In contrast, access to other amino alcohols requires efficient enantioselective routes.[5] Among the numerous synthetic methods developed, there are only a few methods typically employed to prepare chiral amino alcohols.[6,7] In particular, we are interested in the preparation of 2-amino, 2-phenyl ethanols, and their 2-amino-1-phenyl regioisomers.

Recently, some new methods for the preparation of 1,2-amino alcohols have been reported.[8] Their synthetic efficiency is very high considering both regio- and stereoselectivity. Nevertheless, the possibility of exploiting the enantioselectivity that Nature can provide suggests a different approach to their synthesis.

2. Results and discussion

We have previously reported a very effective biocatalyst that can transform styrene derivatives into the corresponding epoxides.[9] This biotransformation produces highly enantioenriched compounds, that possess the correct reactivity for the next synthetic step, that is the reaction of the electrophilic epoxy group with a nucleophilic partner (Fig. 1). In this case, the reactivity at the benzylic position greatly favors nucleophilic addition, thus making the preparation of the 2-phenyl, 2-amino ethanols relatively straightforward. In contrast, the approach of the nucleophile at the less reactive site can be problematic.

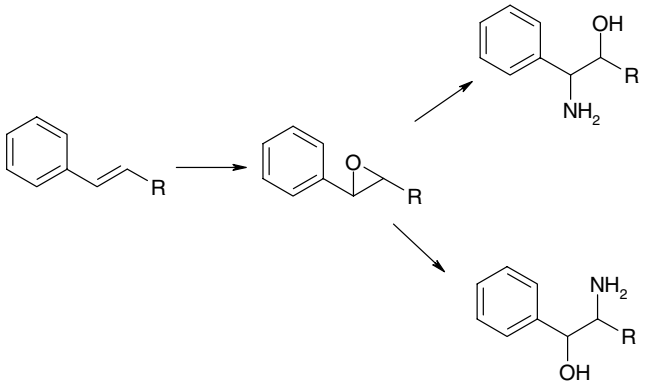

Figure 1. Regioisomeric addition of nitrogen to epoxides.

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In the literature there are some methods, which have been used to regioselectively prepare 2-amino-1-phenyl ethanols from epoxides. However, they show either low productivity or utilize complex reaction procedures. The only papers reporting an efficient method of preparing these compounds employ microwave activation under different conditions.[10] In addition, no preparation of 2-amino-1-phenyl propanol from the corresponding epoxide has been reported. Stimulated by these findings and interested in the enantioselective production of 1,2-amino alcohols, we investigated the possibility of their preparation.

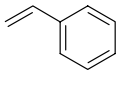
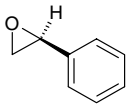
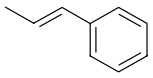
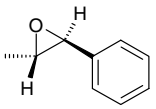
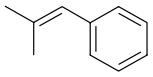
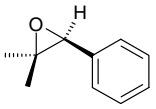
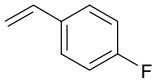
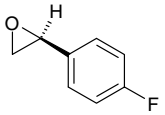
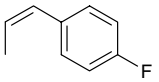
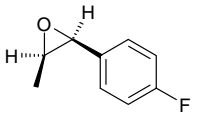
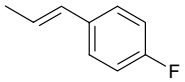
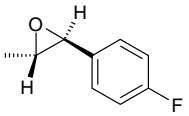
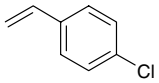
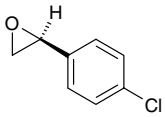
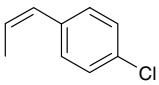
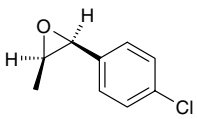
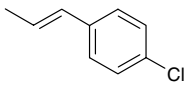
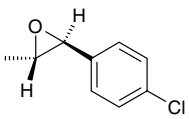
The first step in our synthetic plan is the enzymatic oxidation of styrene derivatives. This was accomplished using a whole cell biocatalyst: a recombinant *E. coli* containing the monooxygenase activity from *P. fluorescens* ST [*E. coli* JM109(pTAB19)]. Bioconversions were performed in a water buffer using an organic phase to separate both the starting hydrocarbon and the epoxide produced. Conversion rates depend on the substrate and are reported in comparison with styrene reactivity in Table 1. All the epoxides obtained are enantiopure, except the epoxide derived from 1-phenyl, 2-methyl propene that shows a small amount of the second enantiomer (~7%). Compound characteristics are in full agreement with literature data.

The second step in the synthetic plan involves the reaction of a nitrogen nucleophile with the epoxide. The reaction of styrene oxides with a nitrogen nucleophile at the benzylic position is a well-known and efficient process;[11] it is commonly performed in two steps. First an azide derivative opens the three-membered ring to give the 1,2-azido alcohol, then the azido group is catalytically hydrogenated to the amino alcohol. Yields are good, and regio- and stereospecificity is nearly complete (Fig. 2).

In contrast, the preparation of the other regioisomer is less straightforward. Notwithstanding the reported methods, the reaction has proven troublesome in our hands. The direct use of ammonia as a nucleophile gives quite a low yield of monoderivative (~30%), always accompanied by the secondary amine. In addition, the use of the Gabriel synthesis was not successful. Looking in the recent literature we found two reports where the use of microwaves was cited as an important factor to improve the yield. We did not try to replicate the result by Favretto et al.,[10a] because it requires special equipment. Moreover, our attempts to replicate the result by Sabitha et al.[10b] (epoxide in the presence of CH_3COONH_4, microwave activation, and no solvent) were unsuccessful. Consequently, we developed a modified procedure. By reacting a water ammonia solution and the epoxide in a closed container under microwave activation, using a commercial home microwave oven, it was possible to synthesize, in good to optimal yield, the desired compound (Fig. 3).

This reaction was applied to some 4-substituted styrene epoxides, obtaining the desired regioisomer as the only isolated product together with some unreacted starting

Table 1. Substrates, products, and relative activity, of the bioconversion of styrene derivatives

Substrate	Product	Relative activity (%)[a]	ee[b]
 **1a**	 **1d**	100	>95
 **1b**	 **1e**	166	>95
 **1c**	 **1f**	310	87
 **2a**	 **2d**	237	>95
 **2b**	 **2e**	38	>95
 **2c**	 **2f**	17	>95
 **3a**	 **3d**	145	>95
 **3b**	 **3e**	78	>95
 **3c**	 **3f**	16	>95

[a] Relative activity = [Specific activity of substrate (*i*)]/[Specific activity of styrene] × 100; Specific activity of (*i*) = mmol of products formed in 1 h by 1 g of cells (dry cell weight) in 1 L of broth, as calculated from the correlation line of the first conversion hours.

[b] Enantiomeric excess was measured by chiral GLC.

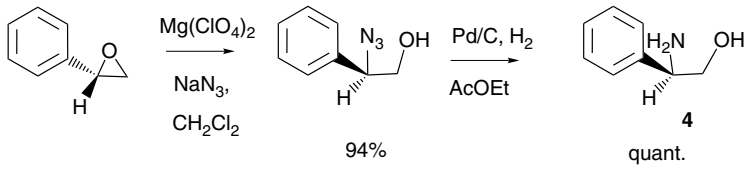


Figure 2. Amino alcohol preparation via azide addition and reduction.

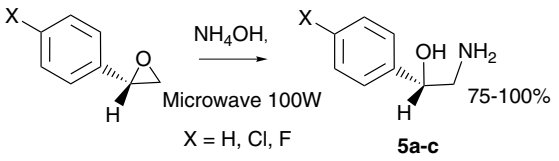


Figure 3. Reaction of monosubstituted epoxides with NH_3 under microwave activation.

compounds. The reaction is very easy because product isolation and purification is straightforward, requiring simple solvent (AcOEt) extraction and solvent evaporation. Interestingly, we did not find the presence of the 1,2-diol that could have also been produced.

Successively, we applied the reaction to 1,2-disubstituted epoxides. In particular, we used the epoxide derived from *trans*-β-methyl styrene. Unexpectedly, the recovered product was the 3-amino, 3-phenyl 2-propanol; the yield obtained was very good (~75%).[12]

This reaction has also been applied to compounds **1f**, **2e**, **2f**, **3e**, and **3f**. The results obtained have proven very interesting: from *trans*-epoxides **2f** and **3f** we obtained the expected 3-amino, 3-phenyl, 2-propanols;[13] in contrast, from *cis*-epoxides **2e** and **3e**, the products were the regioisomeric 2-amino, 1-phenyl, 1-propanols (Fig. 4). The complementary regioisomers were not visible by using ^1H NMR. Finally, from **1f** we obtained the 1-amino, 1-phenyl, 2-methyl, 2-propanols (50%), together with the diol (15%), and the unreacted epoxide (35%).

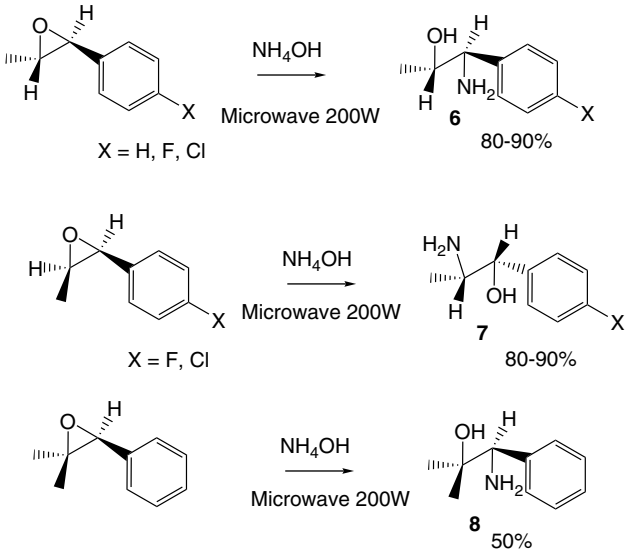


Figure 4. Reaction of α,β-disubstituted and α,α,β-trisubstituted epoxides with NH_3 under microwave activation.

Concerning the diastereoselectivity, the enantiomeric excess present in the reactants is clearly unchanged by the reaction of aminolysis at the homobenzylic position, because the only stereocenter present is not affected by the reaction. We can thus prepare enantiopure 2-amino, 1-phenyl ethanols in two highly selective synthetic steps.

In the case of the epoxide reaction at the benzylic position, the opening reaction could be partly selective, with a retention and inversion of configuration, giving rise to partial racemization. As a matter of fact, we never noticed this evidence. All the reactions proceeded smoothly with total inversion of configuration. This was expected in the azidolysis reaction but, it was also evident that the aminolysis was completely stereoselective. Thus, we can also prepare enantiopure 2-amino, 2-phenyl ethanols.

3. Conclusion

In conclusion, we were able to prepare 2-amino, 1- and 2-phenyl ethanols in good yields and very high enantiopurities coupling the enzymatic preparation of enantiopure phenyl epoxides with selective chemical ring opening by nitrogen nucleophiles under convenient conditions. This approach can be extended to the synthesis of many interesting compounds.

4. Experimental

4.1. Analytical methods

Bioconversion progress was followed by gas chromatography (DANI 86.10 gas chromatograph with FID) on a Chrompack Cp-Sil 8CB column ($T = 100 \pm 150$ °C at 15 °C min, splitless injection) with the appropriate internal standard (dodecane or hexadecane). At intervals, 2 mL samples were taken from the reaction emulsion. The two phases were separated by filtration. The water phase was followed by HPLC on a Merck/Hitachi (L-6200) system connected to a UV-detector set at 230 nm on a (C18 Hibar Lichrosorb 50334, 5 μm, 25 cm) column with 50:50 CH_3CN/water. The absolute (*S*)-configuration of biocatalytically prepared (*S*)-styrene oxide was proven via comparison with commercially available, enantiopure (*S*)-styrene oxide (Aldrich). Based on the analogous chromatographic behavior of racemic mixtures, we assumed an (*S*)-configuration for all epoxides.

The enantiomeric excesses of epoxides and amino alcohols were measured using a Chrompack Chiral-Dex-CB column by comparison to synthetic racemic mixture. Optical rotations were measured with a Perkin Elmer 341 polarimeter. NMR spectra were recorded on a Bruker AC 200 (^{1}H NMR at 200 MHz). All signals are expressed as parts per million down field from tetramethylsilane. All the compounds show spectra in agreement with the literature data.[14]

4.2. Biocatalyst preparation and bioconversion procedure

Biocatalyst *E. coli* JM109 (pTAB19) was prepared by adding 1 mL of an overnight LB culture in 100 mL M9 medium containing: glucose 10 mM; thiamine 0.05 mM; kanamycin 50 μg/mL; IPTG (isopropyl-β-D-thiogalactopyranoside) 1 mM as inducer; and incubated overnight on a shaker at 30 °C. After the growth, OD 1.2–2.0 (λ 600 nm), the cells were separated by centrifugation (10,000 rpm, 4 °C) and added to 70 mL of M9 medium containing glucose (10 mM) on a shaker at 30 °C; the bioconversion was started by adding the substrate (concentration of 10 g/L in the organic phase) dissolved into 30 mL of isooctane (or isooctane/isopropyl ether 9:1 mixture when appropriate). The transformation was carried out at 30 °C.

4.2.1. General procedure for chemical preparation of alkenyl substrates. Methyl (or ethyl)-tri-phenyl phosphonium iodide (20 mmol), 25 mmol of potassium carbonate, 20 mmol of the aldehyde were added to 20 mL of dioxane containing a small amount of water; the solution has been refluxed under agitation for 5–7 h, or until the substrate disappears. The mixture was then filtered to eliminate the salts, dried on Na_2SO_4, and evaporated at reduced pressure very cautiously to avoid material loss. The products were purified by silica gel chromatography to eliminate tri-phenyl phosphine oxide and used in the bioconversions.

4.2.2. General procedure for chemical preparation of racemic epoxides. The olefin (2 mmol) in 10 mL of CH_2Cl_2 was mixed with an equal amount of water containing 1 g of $NaHCO_3$; to this solution was cautiously added 2.2 mmol of 3-chloroperbenzoic acid. The reaction mixture was stirred at rt for 2.5 h, or until the substrate disappeared. Afterwards it was washed with 10 mL of an Na_2SO_3 (1.3 g) water solution for 20 min; the water phase was then extracted with 2×10 mL portions of CH_2Cl_2. The organic phases were washed with 2×25 mL portions of the $NaHCO_3$ water solution and with water. The CH_2Cl_2 phase was dried over anhydrous $MgSO_4$ and evaporated at reduced pressure.

4.2.3. General procedure for MW activated aminoalcohol preparation. Epoxide (20–30 mg) and 5 mL of 33% NH_3 were placed in a 20 mL closed vial. The vial was put in a standard household microwave oven at the chosen power (100–200 MW) for the required time (between 6 and 20 min in 2 min steps). After cooling, the solution was extracted with AcOEt and the organic layer separated and dried over Na_2SO_4. The solvent was evaporated under vacuum.

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