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Synthesis of enantiopure amino alcohols by ring-opening of epoxyalcohols and epoxyethers with ammonia

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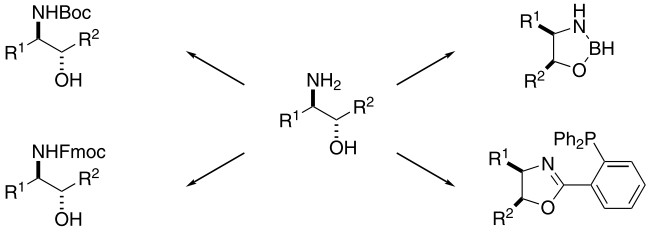
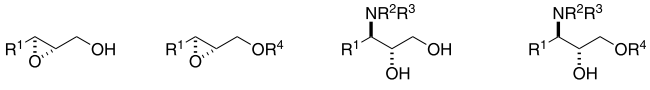
Abstract—Arylglycidols and their corresponding ethers undergo regioselective ring-opening with aqueous ammonia in the presence of organic co-solvents (isopropanol or 1,4-dioxane) to afford 1,2-amino alcohols in high yield.

Chiral enantiopure amino alcohols are attractive compounds, either as ligands for asymmetric catalysis[1] or as building blocks for the preparation of biologically active molecules.[2] Among them, those bearing a free amino group present the opportunity of employing different protecting group strategies (e.g. *N*-Boc or *N*-F-moc), in the synthesis of biomolecules or, when dedicated to catalysis to being the starting materials for the preparation of important types of catalytic ligands such as oxazaborolidines,[3] bis(oxazolines),[4] or phosphinooxazolines.[5]



A very common method for preparing *N*-unprotected 1,2-amino alcohols has been the addition of organometallic species onto the carboxyl group of natural amino acids.[6] This method, however, provides only access to a limited set of amino alcohol structures. To overcome this limitation, we have developed methods for the stereospecific synthesis of enantiomerically pure β-amino alcohols (**3**, **4**) through the regioselective and stereospecific ring opening of epoxyalcohols (**1**) or epoxyethers (**2**) arising from the Sharpless[7] epoxidation.

We have subsequently shown that 3-amino-1,2-diols (**3**) are highly versatile intermediates for the enantioselective synthesis of amino acids[8] and other interesting biomolecules,[9] and that properly substituted amino alcohols (**4**) represent an interesting class of highly modular chiral ligands.[10]



Whenever the preparation of amino alcohols containing unprotected amino groups has been required, two different two-stage procedures have been used according to common practice. In one of these procedures, benzhydrylamine has been employed as the source of the amino group, and the unmasking of the amino function has subsequently required hydrogenolysis of the doubly benzylic carbon–nitrogen bond. In the other approach N_3^-, either in the form of diisopropoxytitanium diazide or as sodium azide in the presence of lithium perchlorate, has been the source of the amino group, again with the need for reduction of the intermediate organyl azide.

Whereas the use of benzhydrylamine as a source for amino groups is clearly uneconomic in atomic terms, the use of azide for the same purpose introduces some degree of risk in the resulting sequences. Bearing in mind the importance of enantiopure amino alcohols, the search for greener alternatives for this considered synthetic operation, involving a more rational use of resources or avoiding the use of potentially dangerous

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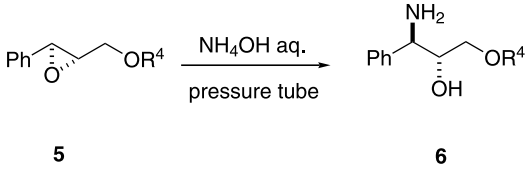
reagents is fully warranted. In line with these ideas, we wish to report here on the development of a safe and straightforward procedure for the regioselective and stereospecific synthesis of amino alcohols from arylglycidols and ethers, involving the use of inexpensive aqueous ammonia as the sole reagent and isopropyl alcohol or 1,4-dioxane as reaction co-solvents.

Although the possibility of preparing amino alcohols by ring-opening of epoxides with ammonia is discussed in textbooks, the use of this reaction for synthetic purposes is scarce.[11] Thus, even terminal epoxides are reported to be attacked slowly by ammonia in the absence of special activation, while most examples with disubstituted epoxides refer to situations where an adjacent carbonyl group activates the ring-opening process.[12] In any case, no example of ring-opening with ammonia of a non-terminal epoxyalcohol or epoxyether has been reported in the literature.[13]

For the initial attempts of direct ring-opening of these substrates, we reasoned that the use of the water-compatible lanthanide triflates introduced by Kobayashi[14] in conjunction with aqueous ammonia could greatly facilitate the reaction by Lewis acid activation of the epoxide. Epoxyethers **5a–d** were used as substrates for these reactions (Scheme 1) and, for solubility reasons, a co-solvent was also used.



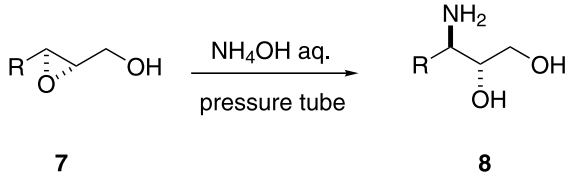
5 6

Scheme 1. Ring-opening of phenylglycidyl ethers **5** with aq. ammonia.

Table 1. Ring-opening of phenylglycidyl ethers **5** with aqueous ammonia

Entry	Product	R^4	Reaction conditions	Yield (%)
1	**6b**	$CHPh_2$	MeOH, $Yb(OTf)_3$, 85°C, 7 h	49
2	**6b**	$CHPh_2$	^{i}PrOH, $Yb(OTf)_3$, 85°C, 20 h	61
3	**6b**	$CHPh_2$	^{i}PrOH, 80°C, 23 h	71
4	**6a**	Me	^{i}PrOH, 85°C, 15 h	95
5	**6c**	CPh_3	1,4-dioxane, 85°C, 60 h	82[a]
6	**6d**	Si^iPr_3	^{i}PrOH, 80°C, 17 h	60[b]

[a] Conversion was 83%.
[b] Conversion was 74%.



7 8

Scheme 2. Ring-opening of epoxyalcohols **7** with aqueous ammonia.

The results and reaction conditions employed for these reactions[15] are summarized in Table 1.

Interestingly, when the benzhydryl ether of phenylglycidol (**5b**) was heated for 7 h at 85°C in ammonium hydroxide/methanol in the presence of a 0.15% equiv. molar amount of ytterbium triflate (pressure tube) regioselective ring-opening took place, and amino alcohol **6b** was obtained in 49% yield. Under these conditions, methanol competed with ammonia as the nucleophile, and 3-benzhydryloxy-1-methoxy-1-phenylpropan-2-ol arising from C-3 attack was also obtained (10% yield). To avoid this problem, the use of a less nucleophilic co-solvent was considered. Changing to isopropanol (entry 2) led to an increase in the yield of **6b**, but with longer reaction time. At this stage, in order to analyze the relative importance of the Lewis acid on the reaction course, we decided to perform the reaction without adding the ytterbium salt (entry 3). To our surprise, the reaction rate showed no decrease, **6b** being obtained in an optimal 71% yield with complete regiocontrol.

The same reaction conditions were subsequently applied to **5a**, **5c** and **5d**. In the case of **5c**, 1,4-dioxane was used as a co-solvent instead of isopropyl alcohol to improve substrate solubility. As can be observed in Table 1 (entries 3–6) the reactions took place very cleanly, leading in high yield to amino alcohols **6a–d**. The regioselectivities in these ring-opening reactions were in all cases very good, with no C-2 ring-opened products being detected (analysis by ^{13}C NMR). Moreover, since no *syn* diastereomers of the amino alcohols **6** could be detected by ^{13}C NMR, and the enantiomeric purity of amino alcohols **6a–d** was coincident with that of the starting phenylglycidyl ethers **5a–d** (>99%), the ring-opening reactions are stereospecific. When R^4 was a rather bulky protecting group, the process turned out to be slower and some starting material was recovered (entries 5 and 6). Conversely a very high yield was recorded for the substrates bearing a non-bulky R^4 group. All reaction products were fully characterised by ^1H and ^{13}C NMR data and by comparison with the known compounds[16] obtained via the indirect, two-stage procedure.

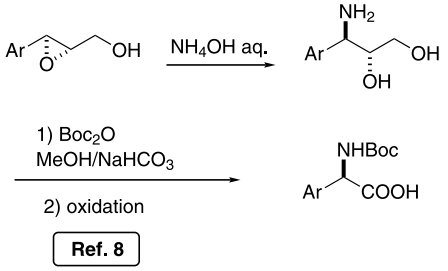
Also interesting is the direct ring-opening of epoxyalcohols with ammonia, since the resulting aminodiols could be transformed in a very straightforward and practical manner, following our previously described methodology,[8a,c] into a variety of biologically important amino acids and dipeptide isosteres. Accordingly, epoxyalcohols **7a–c** were evaluated in this epoxide-opening process (Scheme 2). The results obtained in these experiments are summarized in Table 2.

Again in this case, the reactions carried out on arylglycidol substrates took place stereospecifically and with complete regioselectivity leading to the target

Table 2. Ring-opening of epoxyalcohols **7** with aqueous ammonia

Entry	Product	R	Reaction conditions	Yield (%)
1	**8a**	Phenyl	^{i}PrOH, 70°C, 18 h	86
2	**8b**	Mesityl	^{i}PrOH, 80°C, 20 h	71[a]
3	**8c**	Biphenyl-4-yl	1,4-Dioxane, 80°C, 23 h	95

[a] Conversion was >95%.



Scheme 3. Three-step synthesis of enantiopure arylglycines.

aminodiols[17] in good yield. As already noted for phenylglycidyl ethers (Table 1) the reaction is somewhat sensitive to steric hindrance near the epoxide ring, and mesitylglycidol **7b** underwent ring-opening at a slightly slower rate despite of the strong electron donating nature of the mesityl substituent.

On the other hand, and not unexpectedly when the reaction was attempted on an aliphatic substrate such as (2*S*,3*S*)-2,3-epoxyhexanol the process was not as effective and was poorly regioselective. Thus, after heating the reaction mixture at 85°C for 60 h under the standard reaction conditions a mixture of regioisomeric aminodiols was obtained in low yield (29%). The benzylic nature of the carbon atom being attacked thus appears to be a requisite for the reaction to proceed.

In summary, the ring-opening of arylglycidyl ethers and arylglycidols with aqueous ammonia is a feasible reaction; it takes place stereospecifically and with complete regiocontrol, and provides a convenient alternative to the classical two-stage sequences involving either poorly atom-economic conditions or the use of potentially hazardous reagents. Bearing in mind both the potential uses in catalysis of the amino alcohols derived from arylglycidyl ethers, and the interest in arylglycines with aromatic groups covering a range of electronic or steric characteristics, it is to be expected that the newly developed procedure will find, for its simplicity and sustainable characteristics, ample application among synthetic chemists.

As a simple illustration of its potential, the integration of the aqueous ammonia-mediated regioselective ring-opening of enantiopure arylglycidols into well established synthetic schemes for the preparation of protected arylglycines[8] renders these products available in three simple steps and high overall yield (Scheme 3).

Acknowledgements

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15. Representative experimental procedure: Epoxide, NH_4OH (aprox. 40 equiv. of a 30% solution in water) in ^{i}PrOH (volume NH_4OH/volume ^{i}PrOH, 1/2) were stirred in a sealed tube at the temperature specified and the time indicated in Table 1 or Table 2. The solution was concentrated in vacuo and purified by chromatography through an SiO_2 column with hexane /EtOAc as eluent.
16. See Ref. 10b. Compounds **5d**, (2*S*,3*S*)-3-phenyl-2,3-epoxy-1-triisopropylsilyloxypropane and **6d**, (1*R*,2*R*)-1-amino-1-phenyl-3-triisopropylsilyloxypropan-2-ol are new compounds and gave satisfactory IR, ^{1}H, ^{13}C NMR and MS data.
17. Since aminodiols **8a** and **8b** are highly polar compounds they were purified by chromatography through a SiO_2 column with AcOEt/MeOH. Epoxide **7c** was prepared as a racemate. Due to its high insolubility aminodiol **8c**, which was obtained in a relatively pure form, was directly transformed into its diastereomerically pure (^{13}C NMR) *N*-Boc derivative. All new compounds gave satisfactory ^{1}H and ^{13}C NMR data.