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REGIOSELECTIVE RING OPENING OF CHIRAL EPOXYALCOHOLS BY PRIMARY AMINES

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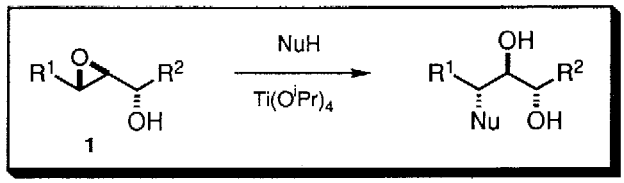
Summary: *A reinvestigation of the titanium(IV)-mediated reaction of primary amines with chiral 2,3-epoxyalcohols shows that, contrary to previous reports, this reaction constitutes a general and practical process for the enantioselective synthesis of 3-amino-1,2-diols.*

Since the introduction by Sharpless and co-workers of the asymmetric epoxydation of allylic alcohols,[1] chiral epoxyalcohols **1** have become a most useful building block for the stereocontrolled synthesis of complex molecules.[2]

One of the usual ways for the integration of **1** into synthetic sequences involves the titanium(IV) mediated regioselective ring opening by nucleophiles, a process also disclosed by Sharpless.[3] In this way, two or three adjacent chiral centers can be constructed in a stereocontrolled manner by operationally simple methodology.



The 3-amino-1,2-diol array, which could conveniently arise from the reaction of **1** with primary amines able to experience a subsequent cleavage leaving a free amino group, is perhaps the most attractive one among those directly derivable from the reaction. However, while a variety of secondary amines have been shown to open efficiently 2,3-epoxyalcohols in the presence of titanium tetraisopropoxide,[3,4] there are no reports in the literature concerning the successful use of primary amines in a similar reaction. In fact, Caron and Sharpless reported[3] that the reaction of 2,3-epoxyhexanol with *n*-butylamine failed to give any identifiable product. These negative results have probably oriented the research in this area to the use of the less convenient azide anion as a synthetic equivalent for ammonia.[3,5]

We have now re-examined the reaction of chiral epoxyalcohols with a variety of primary amines finding that a clean ring opening takes place in a highly regioselective manner.

The epoxyalcohols **1a-c**, covering a wide range of steric and electronic differentiation of C_2/C_3 towards nucleophilic attack, were selected as substrates. The primary amines **2** used for the ring opening study were selected either to provide information on the influence of steric effects on the regioselectivity of the reaction (**2a**, **2b**) or to afford ring opened compounds readily amenable to amine deprotection (**2c**, **2d**, **2e**).

1a $R^1 = C_6H_5$
1b $R^1 = CH_3$
1c $R^1 = CH_3CH_2CH_2$

$R^2\text{-}NH_2$

2a $R^2 = n\text{-}C_6H_{13}$
2b $R^2 = tert\text{-}butyl$
2c $R^2 = Ph_2CH$
2d $R^2 = PhCH_2$
2e $R^2 = p\text{-}MeOC_6H_4CH_2$

After securing that the ring opening does not proceed (or proceeds at a very low rate) in the absence of titanium(IV), the reactions were performed in CH_2Cl_2 solution with molar ratios of **1** / **2** / $Ti(O^iPr)_4$ in the range of 1 / 1.2-1.5 / 1.2-3, the disappearance of **1** being followed by TLC. Usual work up afforded essentially pure aminodiols **3**. The regioselectivity of the reaction was easily monitored by ^{13}C NMR spectroscopy.

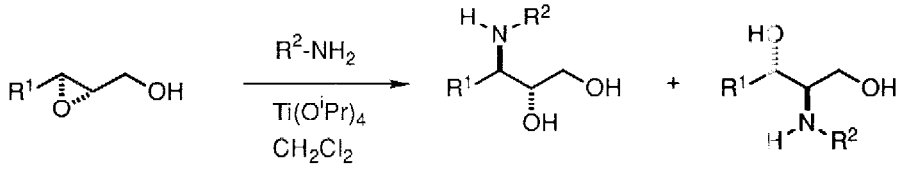


TABLE : TITANIUM-MEDIATED RING OPENING OF 2,3-EPOXYALCOHOLS BY PRIMARY AMINES[6,7]

	 **1a**	 **1b**	 **1c**
$n\text{-}C_6H_{13}\text{–}NH_2$ **2a**	12 h, r. t. C_3 83 % **3aa**	72 h, reflux C_3/C_2 : 93/7 96 % **3ba**	408 h, r. t. C_3/C_2 : 92/8 51 % **3ca**
$(CH_3)_3C\text{–}NH_2$ **2b**	12 h, r. t. C_3 64 % **3ab**	12 h, r. t. C_3/C_2 : 94/6 18 % **3bb**	192 h, r. t. C_3/C_2 : 88/12 57 % **3cb**
$Ph_2CH\text{–}NH_2$ **2c**	2 h, r. t. C_3 76 % **3ac**	30 h, r. t. C_3/C_2 : 97/3 76 %* **3bc**	72 h, reflux C_3/C_2 : 94/6 70 % **3cc**
$PhCH_2\text{–}NH_2$ **2d**	5 h, r. t. C_3 57 % **3ad**	96 h, r. t. C_3/C_2 : 94/6 55 % **3bd**	264 h, r. t. C_3/C_2 : 97/3 70 % **3cd**
MeO–  –CH_2NH_2 **2e**	8 h, r. t. C_3 72 % **3ae**	99 h, r. t. C_3/C_2 : 95/5 53 % **3be**	264 h, r. t. C_3/C_2 : 92/8 80 % **3ce**

* *In situ* opening, overall yield (see text)

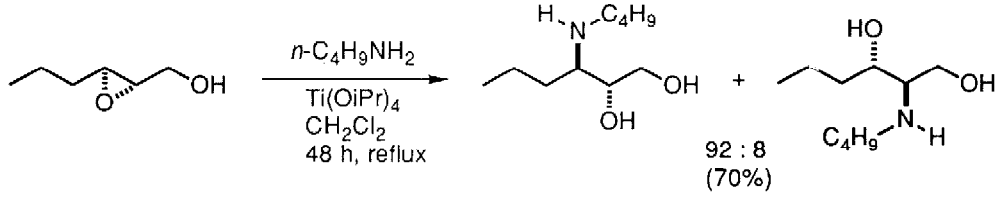
When enantiomerically pure (-)-**1a** was submitted to the forementioned reaction conditions, a fast ring-opening took place at room temperature (see Table). Within the limits of ^{13}C NMR detection, aminodiols **3aa-3ae** were obtained as a single regioisomer resulting from C_3 attack. As an example, the enantiomeric purity of **3ae** was tested by ^1H and ^{19}F NMR study of the corresponding Mosher diesters,[8] As anticipated, a single set of signals was observed.

For the study of the ring opening of **1b**, the more readily available racemic form was used. The reactions were generally slower than with **1a** and, although highly regioselective, gave rise to minor amounts of the regioisomer derived from C_2 attack. The initially low yields recorded in these reactions induced additional work directed towards the optimization of reaction conditions. Two parameters were analyzed: reaction temperature and time of hydrolysis of the titanate intermediates. Although the yield of **3bb** could not be improved, the preparation of **3ba** could be achieved in essentially quantitative yield by performing the reaction under CH_2Cl_2 reflux and extending the time of hydrolysis. It is worth noting that **3ba** was obtained in only 56% yield when the reaction was performed at room temperature and the reaction crude submitted to standard hydrolysis. The regioselectivity was exactly the same under both sets of reaction conditions.

The preparation of **3bc** provides a further example of the influence of reaction conditions on the yield of the reaction. Thus, *in situ* ring opening of (-)-**1b** with **2c** led to **3bc** (same enantiomeric purity as **1b**) in 76% overall (epoxydation + ring opening) yield. Conversely, ring opening of pure racemic **1b** required a longer reaction time (30 *vs.* 12 hours) and took place with lower (48 *vs.* 76%) yield.

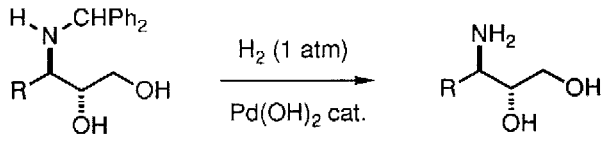
Finally, the ring opening of **1c** was studied on the (-)-enantiomer as obtained by catalytic Sharpless epoxidation. In spite of the increased steric hindrance for C_3 attack, the process exhibited approximately the same regioselectivity than with **1b**. Even with the bulky *tert*-butylamine (**2b**), aminodiol **3cb** was obtained as a 88 / 12 mixture of regioisomers, C_3 attack being favoured. The main effect of the increased bulk of the C_3 substituent was an important lowering of reaction rates (see Table). However, reaction times could be substantially shortened by performing the reactions at reflux without any loss in regioselectivity. On the other hand, ^1H and ^{19}F NMR analysis of the Mosher diesters[8] of **3cc** showed an enantiomeric purity fully coincident with that described for the catalytic Sharpless epoxidation of (*E*)-2-hexen-1-ol.[1b]

The overall good results recorded with **1c** led us to think that the negative results recorded by Caron and Sharpless[3] in the reaction of this epoxyalcohol with *n*-butylamine could perhaps be due to some uncontrolled experimental factor. In our hands, the reaction took place very cleanly leading to the expected 3-amino-1,2-diol with 70 % yield.



In summary, we have shown that, contrary to previous reports, *the titanium(IV) mediated ring opening of epoxyalcohols with primary amines is a feasible reaction that takes place with perfectly defined stereo- and regiochemistry.* Yields are uniformly high and no by-products are formed along with the desired aminodiols **3**. The synthetic potential of the reaction is illustrated by a short enantioselective synthesis of small ring nitrogen-containing heterocycles presented in the accompanying paper.[9]

If the primary amine involved in the reaction is viewed as a synthetic equivalent for ammonia, benzhydrylamine **2c** turns out to be a most convenient surrogate for NH_3. Besides high yield and strict regiochemical control (see Table), detachment of the diphenylmethyl group can be readily accomplished:



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$R = CH_3$	100%
$R = CH_2CH_2CH_3$	72%

Elaboration of free aminodiols **4** into several types of enantiomerically pure aminoacids and cyclic derivatives is actively pursued in our laboratories and will be reported in due course.

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6. All compounds have been fully characterized and show satisfactory spectral and (for solid compounds) analytical data
7. **Typical experimental procedure**: In a round bottomed flask flushed with nitrogen and equipped with magnetical stirring, reflux condenser and rubber septum, a solution of the epoxide (2 mmol) in 15 mL CH_2Cl_2 was placed. A solution of titanium isopropoxide (4 mmol) in 2 mL CH_2Cl_2 and a solution of the corresponding amine (2.4 mmol) in 2 mL CH_2Cl_2 were subsequently added *via canula* and the mixture was stirred at room temperature or at reflux (see table) the reaction being monitored by TLC. When the reaction was complete, a solution of 10% NaOH in saturated brine (6 mL) was added and the suspension stirred for an additional period of 12 h. The solution was filtered through a short pad of celite and extracted with HCl 0.1 M several times (until no aminodiol could be detected by TLC of the organic phase). The aqueous phase was washed once with CH_2Cl_2, brought to pH 8-9 with 1M NaOH and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated. Residual amounts of non volatile amines were finally removed by chromatography or, in some cases, crystallization.
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