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Enantioselective ring opening of epoxides with trimethylsilyl azide ($TMSN_3$) in the presence of β-cyclodextrin: an efficient route to 1,2-azido alcohols †

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Abstract

The ring opening of epoxides with nucleophiles such as $TMSN_3$ and isopropylamine takes place enantioselectively in the presence of β-cyclodextrin under extremely mild conditions and the azido alcohols and amino alcohols are formed as (*S*)-isomers. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Epoxides are versatile intermediates in organic synthesis as their ring can be easily opened by a variety of nucleophiles, yielding a broad range of valuable products.[1] Enantioselective ring opening of *meso* or racemic epoxides by nucleophilic reagents is one of the most powerful methods in the asymmetric synthesis of 1,2-disubstituted compounds.[2] Among the vast number of nucleophiles that have been employed in the ring opening, azides (which afford the corresponding vicinal azidohydrins) have received considerable attention. The classical reagents for azidohydrin synthesis are the combined use of $TMSN_3$ or sodium azide and a Lewis acid or a transition-metal complex.[3] Further, the vicinal azidohydrins are precursors of β-amino alcohols, which are present in numerous natural products. Recently, Jacobsen reported the asymmetric ring opening of epoxides by using $TMSN_3$ in the presence of a chiral Cr complex.[4] Similarly, the asymmetric ring opening of *meso* epoxides with anilines has been accomplished in the presence of chiral BINOL–Yb triflate complexes and amines.[5]

In the context of our recent studies,[6] it has been shown that liver microsomes can be used in the stereoselective ring opening of epoxides with amines and they have also been opened selectively by various amines in the presence of lipases. The selective ring opening reaction of epoxides with sodium borohydride in the presence of cyclodextrin in aqueous media has also been reported.[7] In the literature, cyclodextrins and macrocyclic compounds consisting of α-1,4-linked D-glucopyranose have attracted much attention, because of their ability to form inclusion complexes.[8,9]

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Based on the above findings, it was considered of interest to investigate the effect of β-cyclodextrin on the ring opening reaction of epoxides with nucleophiles. Herein, we wish to report the stereoselective ring opening reaction with $TMSN_3$ in the presence of β-cyclodextrin in aqueous media to afford 1,2-azido alcohols.

Some of the earlier studies on azidolysis with $TMSN_3$ require high temperature and alkaline conditions in the absence of catalysts, whereas, in some of the recent reports, metal complexes such as Ti(O-*i*-Pr)$_4$,[10a–c] Al(O-*i*-Pr)$_3$,[10b] Yb(O-*i*-Pr)$_3$,[10d] and [Hf(OTf)$_4$, Zr(OTf)$_4$, Yb(OTf)$_3$][10e] have been employed as catalysts for the regio- and chemoselective azidolysis with $TMSN_3$ to afford the corresponding azido alcohols or azido silyl ethers. In the case of azido silyl ethers, they have been hydrolyzed under acidic conditions to yield the desired azido alcohols.

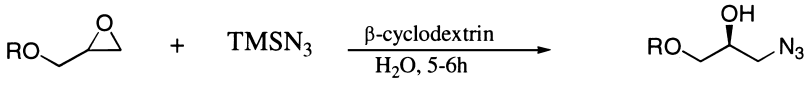
In the present study, the reaction of an epoxide with $TMSN_3$ in the presence of β-cyclodextrin gives a mixture of the ring-opened azido alcohol and the epoxide which has been monitored by HPLC employing a chiral column. The unreacted epoxide and azido alcohol have been separated by column chromatography.

In a typical procedure, 3-phenoxy-1,2-epoxypropane (100 mg, 0.66 mmol) was dissolved in 1 ml of ethanol and to this β-cyclodextrin (1.13 g, in 20 ml water) was added. After stirring for 30 min at room temperature, trimethylsilyl azide (100 mg, 0.86 mmol) was added and incubated at 37°C in an orbital shaker for 5 h. The reaction mixture was then extracted with ethyl acetate and dried over $MgSO_4$. The residue was purified by silica gel column chromatography to give corresponding unreacted epoxide followed by the 1,2-azido alcohol. This method has been found to be applicable to a series of terminal epoxides and the results are illustrated in Table 1.

Table 1
Ring opening of racemic epoxides with $TMSN_3$ in the presence of β-cyclodextrin

Entry	R	Product[a] (Yield, %)[b]	Enantiomeric excess of the (S)-isomer (ee %)[c]	Yield of the recovered epoxide (%)[d]	Enantiomeric excess of the recovered (R)-epoxide (ee%)[c]
1a	C_6H_5	**2a** (45)	84	46	80
1b	(*p*-Cl)C_6H_4	**2b** (38)	64	54	56
1c	(*p*-NHCOCH$_3$)C_6H_4	**2c** (48)	90	45	88
1d	(*o*-OCH$_3$)C_6H_4	**2d** (40)	>99	56	90
1e	(*p*-CH$_2$CH$_2$OCH$_3$)C_6H_4	**2e** (45)	75	43	68
1f	1-naphthyl	**2f** (47)	95	40	90

In all cases studied, the conversion was detected by HPLC, and after about 50% conversion, the reaction mixture was extracted with ethyl acetate. The conversion of these substrates **1a–f** to the corresponding azido alcohols **2a–f** takes place in one-pot as azido silyl ethers are not formed (Scheme 1). It is observed from the results that the (*S*)-isomer is formed predominantly. Interestingly, when these epoxide ring opening reactions have been performed using NaN_3, significant enantioselectivity has not been observed.



Scheme 1.

This method is applicable to various epoxides having different substituents on the aryl ring of the phenoxy group. The absolute configuration has been assigned based on earlier literature studies,[11] by employing a Chiralcel OD column and unambiguous synthesis to the corresponding known β-blockers. Further, this study has been extended to the ring opening of racemic epoxides with isopropylamine in the presence of β-cyclodextrin. Also, in this reaction the (*S*)-isomer of the product is observed predominantly and the results of this investigation are described in Table 2.

Table 2
Ring opening of racemic epoxides with isopropylamine in the presence of β-cyclodextrin

Entry	R	Product[a] (Yield, %)[b]	Enantiomeric excess of the (S)-isomer (ee %)[c]	Yield of the recovered epoxide (%)[d]	Enantiomeric excess of the recovered (R)-epoxide (ee%)[c]
1a	C_6H_5	**3a** (48)	90	41	88
1b	(*p*-Cl)C_6H_4	**3b** (45)	86	43	82
1c	(*p*-NHCOCH$_3$)C_6H_4	**3c** (45)	80	47	80
1d	(*o*-OCH$_3$)C_6H_4	**3d** (40)	65	57	59
1e	(*p*-$CH_2CH_2OCH_3$)C_6H_4	**3e** (47)	92	44	89

[a]All the compounds have been characterized by ^{1}H NMR, IR spectroscopy, mass spectrometry and gave satisfactory elemental analysis.
[b]Isolated yields.
[c]Determined by chiral HPLC (chiralcel OD column, Daicel) employing hexane-isopropanol (85:15) with 0.1% diethyl amine as mobile phase, 0.5 ml/min flow rate and monitored at 254 nm wavelength.
[d]Determined by HPLC.

In summary, we have developed a synthetically useful and practical approach for the preparation of enantiomerically enriched azido alcohols in one-pot by the opening of racemic epoxides with $TMSN_3$ in the presence of β-cyclodextrin in aqueous medium. This method has potential for the preparation of non-racemic 1,2-amino alcohols of biological interest. In addition, the enantioselective opening of epoxide with $TMSN_3$ takes place under extremely mild conditions and is expected to have wide applicability.

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