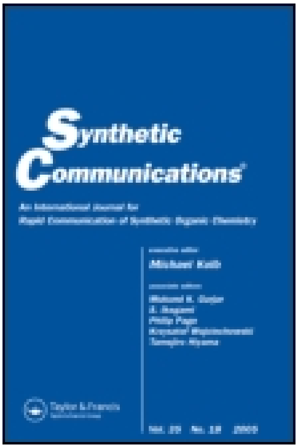

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Regioselective Cleavage of Epoxides: Conversion of Racemic Epoxides to Optically Active Alcohols

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REGIOSELECTIVE CLEAVAGE OF EPOXIDES: CONVERSION OF RACEMIC EPOXIDES TO OPTICALLY ACTIVE ALCOHOLS

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Abstract: Regioselective reduction of racemic epoxides to optically active alcohols using chirally modified zirconium tetrachloride - sodium borohydride with L-proline.

Epoxides are versatile reactive intermediates from which diols, ketones or alcohols could be obtained with appropriate reagents. Reductive cleavage of epoxides is an important method of making alcohols. In our continuous interest on the studies of new chiral auxiliaries we have investigated the reaction of epoxides with zirconium tetrachloride - sodium borohydride[1] in the presence of a L-proline as a chiral auxiliary.

We report the regioselective reduction of racemic epoxides (1a-f) to optically active alcohols (2a-f) [Scheme-I].

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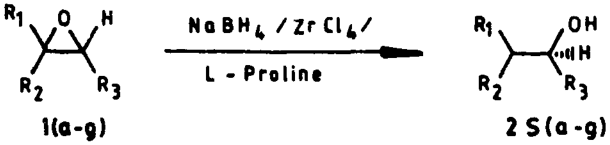
Scheme I



The epoxides were prepared from the corresponding olefins by standard methods using either m-chloro perbenzoic acid or t-butyl hydroperoxide. A typical procedure for the reduction involved the addition of epoxide to a suspension of chirally ligated zirconium tetrachloride - sodium borohydride [The reagent was prepared by the addition of sodium borohydride to a solution of zirconium tetrachloride in anhydrous tetrahydrofuran under an inert atmosphere followed by the addition of L-proline and stirred for 24 hours] at 0°C. The reaction mixture was quenched with 20% HCl solution and extracted with ethyl acetate to give alcohols of reasonably good optical purity and excellent chemical yields. The crude product was purified by column chromatography . The results are tabulated in table I. The configuration of the alcohols thus obtained was found to be 'S' by the correlation with the reported sign of rotation. The present observation is highly significant as this is the first report on the formation of asymmetric alcohols from racemic epoxides, even though the enantiomeric purity of the alcohols obtained are not high.

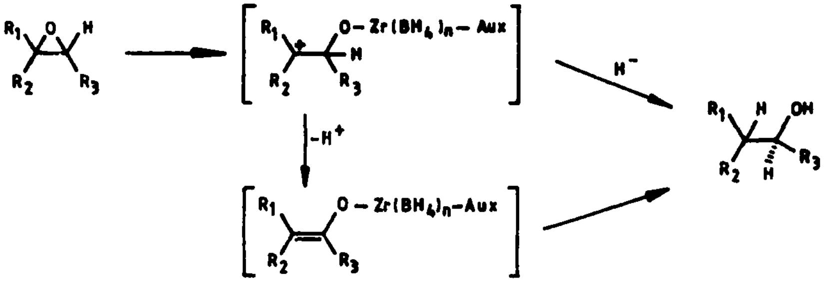
The reaction of zirconium tetrachloride - sodium borohydride with epoxide could possibly proceed by an initial conjugation of zirconium with the epoxide. The zirconium conjugate could undergo C-O bond scisson with the concommitant loss of proton from the α-carbon leading to a zirconium enolate which could be reduced further to the alcohol. The observed enantioselectivity in the reduction of epoxides could arise because of the possible differentiation of the re and si faces of the enolate by the reducing agent. On the other hand a direct hydride transfer to the zirconium

Table I:

Sl.	Substrate(1)			Product (2)			Time	Yield (%)		Config.
No.	R_1	R_2	R_3	R_1	R_2	R_3	(hrs)	Chem	% e.e	
a	CH_3	$-(CH_2)_4-$		CH_3	$-(CH_2)_4-$		3	60	44.2[4]	(1R,2S)
b	Ph	H	Ph	Ph	H	Ph	3	45[7]	21.7[5]	S
c	H	Ph	Ph	Ph	H	Ph	3	80	4.5[5]	S
d	Ph	H	CHO	Ph	H	CH_2OH	24	80	7.6[2]	S
e	Ph	CH_3	H	Ph	CH_3	H	3	80	-	-
f	H	H	CH_2Op-tol	H	H	CH_2Op-tol	3	82	-	-
g	Ph	H	CH_2OH	Ph	H	CH_2OH	3	82	-	-

conjugate sequential to the oxirane fission should lead to only racemic alcohol in view of the complete conversion of the epoxide to the product. [Scheme-II]

Scheme II



The zirconium enolate path was substantiated by carrying out the reduction of an optically active epoxide. Reaction of (S)-2,3-epoxy,3-phenyl propanol[7] with zirconium tetrachloride - sodium borohydride gave (S)-1,2-dihydroxy 3-phenyl propane with partial racemization (30% ee). If the reduction were to proceed via a direct hydride transfer path the resulting alcohol should retain the configuration assuming the regioselective opening of the oxirane ring.

The present work provides a method for the preparation of optically active alcohols from racemic epoxides. Further investigations are in progress to improve the enantiomeric purity by suitable modifications in the chiral auxiliary[8].

Experimental:

Anhydrous tetrahydrofuran was distilled over sodium-benzophenone ketal prior to use. The reactions were carried out under a continuous atmosphere of nitrogen.

General procedure for the reduction of epoxides using $NaBH_4/ZrCl_4$ and L-proline as the chiral auxiliary

To a solution of zirconium tetrachloride (1.265g, 0.0054 mol) in 25ml of anhydrous tetrahydrofuran was added sodium borohydride powder (0.811g, 0.0216 mol) at room temperature under an inert atmosphere. After the reaction mixture has been stirred for 30 minutes, L-proline (0.50g, 0.0043 mol) was added and stirring was continued for a further 24 hrs. Into the chiral reducing agent was added a solution of epoxide (0.0034 mol) in 5ml of tetrahydrofuran at 0°C and the mixture stirred until the disappearance of epoxide (by tlc) at room temperature. The reaction was quenched by dropwise addition of 50% hydrochloric acid at $0^{o}C$. The solvent was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3x25 ml). The combined organic extracts were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silica gel >200 m). The products were analysed by ^{1}H-NMR and mass spectra. The % e.e was calculated by comparing with the literature values.

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