

Note

Chirally modified $\text{NaBH}_4/\text{ZrCl}_4$ promoted asymmetric reduction of prochiral ketones[†]

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Enantioselective reduction of prochiral ketones has been achieved by the combination of $\text{NaBH}_4/\text{ZrCl}_4$ and (*S*)-(-)- α,α -diphenyl prolinol in moderate to high enantiomeric excess.

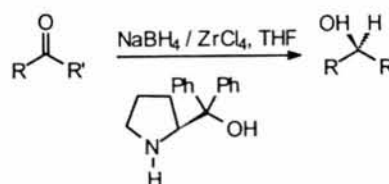
Enantioselective reduction of prochiral ketones has been one of the most actively studied areas in asymmetric synthesis¹. Homochiral alcohol products serve as useful starting materials, for many syntheses and often they are the desired end products of a reaction sequence.

In the recent years the asymmetric reduction of ketones has been intensively investigated by using chiral oxazaborolidine catalyzed reductions and as well as with a few chiral modified LiAlH_4 and NaBH_4 transition metal catalyzed reductions². Particularly, the combination of NaBH_4 - ZrCl_4 coupled with a chiral amino alcohol has been found to be very effective chiral auxiliary, for the high enantioselective reduction of ketoxime-O-alkyl ethers to optically active amines³.

Recently, we have described the potential application of this chiral modifier for the enantioselective opening of the racemic epoxides to their corresponding alcohols⁴. Hence, we set out to extend this study and to explore further scope of this reducing agent as chiral auxiliary for the stereoselective reduction of prochiral ketones.

In this communication we wish to disclose the asymmetric reduction of prochiral ketones with $\text{NaBH}_4/\text{ZrCl}_4$ in the presence of (*S*)-(-)- α,α -diphenyl prolinol⁵ as a chiral auxiliary (**Scheme I**).

The reagent is prepared by combining one equivalent



Scheme I

of ZrCl_4 in dry THF solvent with four equivalents of NaBH_4 followed by the addition of one equivalent of (*S*)-(-)- α,α -diphenyl prolinol. The chiral reagent thus prepared was reacted with different range of prochiral ketones to give the corresponding optically active alcohols in moderate to high enantiomeric excess.

As shown in the **Table I** the acetophenone was reduced to 1-phenyl ethyl alcohol in 25% enantiomeric excess with 95% chemical yield. All the reductions were carried out at room temperature in dry THF solvent. In order to test the generality of the enantioselective reduction, seven representative prochiral ketones (entry 1-7, **Table I**) were taken and subjected to enantioselective reduction under similar reaction conditions. 2-Chloro-1-phenyl-1-ethanone (entry 2) gave 2-chloro-1-phenyl-(1*S*)-ethan-1-ol in 97% isolated chemical yield with 47% enantiomeric purity. A substantial increment in enantioselectivity was observed with an increase in steric crowding around carbonyl functionality. For example, in case of propiophenone (entry 6) on reduction afforded 1-phenyl-(1*S*)-propan-1-ol with 90% chemical yield and with an optical purity of 65%.

Encouraged with the preliminary results the protocol was applied for aliphatic prochiral ketones (entry 5 and 7). When 4-methyl-2-pentanone (entry 5) was subjected to enantioselective reduction it furnished corresponding *S*-isomer, 4-methyl-(2*S*)-pentan-2-ol in 61% ee. A similar result was noted with 3-methyl-2-butanone (entry 7), this provided corresponding *S*-enantiomer with 60% optical purity. This method was tested for the reduction of 1,2-dicarbonyl compound. When 1,3-diphenyl-1,2-propanedione (entry 4) was reduced under similar reaction conditions, to our surprise it furnished 1,3-diphenyl-(1*S*,2*S*)-

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Table I—Asymmetric reduction of prochiral ketones with chirally modified $\text{NaBH}_4/\text{ZrCl}_4$

Entry	Substrate	Product	Yield ^a (%)	ee ^b (%)	Config.
1			95	30	S
2			97	47	S
3			93	89	S
4			89	54	S
5			96	61	S
6			90	65	S
7			92	60	S

^aIsolated yields; ^b e.e (%) refer to measurement of the optical rotation of the isolated compounds and compared with their known optical rotations

propane-1,2-diol with moderate diastereomeric purity of 54%. It is noteworthy to mention that in the series the β -tetralone (entry 3) was reduced in high stereoselectivity (89% ee).

When $\text{ZrCl}_4/\text{NaBH}_4/(S)(-)\text{-}\alpha,\alpha$ -diphenyl prolinol were reacted in THF solvent at room temperature, the reducing species generated is presumably a mixture of zirconium aminoalkoxy borohydrides⁶. In all the experiments conducted the reagent consistently afforded the *S* alcohol exclusively (**Table I**). The optical purity of the alcohols were determined by comparing the optical rotation values to their known authentic samples.

In conclusion we have successfully demonstrated the potentiality of this reagent as an efficient chiral

auxiliary to affect the asymmetric reduction of the prochiral ketones in moderate to high enantioselectivity.

Experimental Section

Optical rotations were measured on JASCO DIP-370 digital Polarimeter. ¹H NMR spectra were recorded on a JEOL FX 9Q FTNMR 200 MHz using TMS as an internal standard.

Typical experimental procedure for the enantioselective reduction—In a typical experiment to a two necked round bottom flask equipped with magnetic bead and nitrogen balloon adaptor was placed ZrCl_4 (0.9g, 7.9 mmol) and dry THF (10 mL) was syringed into the flask. Immediate formation of red brown

solution was observed. The contents were cooled to 0°C, NaBH₄ (1.16g, 31.6 mmol) was added in portion. Red brown solution slowly turned to pale pink. After the complete addition of NaBH₄ the ice cooling was removed and the contents were stirred at room temperature for 1 hr. A solution of (*S*)(-)- α,α -diphenyl prolinol (1.0 g, 7.9 mmol) in anhydrous THF (5 mL) was added to the above mixture at room temperature and the contents were magnetically stirred for 3 hr. To the resulting chiral reducing agent was added acetophenone (0.9g, 7.9 mmol) in THF (5 mL), and the mixture was stirred for 2 hr. The progress of the reaction was monitored by TLC. After the completion of the reaction the mixture was cooled to 0°C and quenched by the dropwise addition of dilute hydrochloric acid (5%). From the reaction mixture THF was evaporated under vacuum and the remaining aqueous layer was extracted with ethyl acetate. The organic layers were pooled, washed successively with brine, water and dried over anhydrous sodium sulfate. Evaporation of solvent followed by purification of the crude product by silica gel column chromatography

gave the corresponding (*S*)(-)-1-phenyl ethyl alcohol [0.87g, 95% $[\alpha]_D^{20}$ -13.5, (*c* = 5 in MeOH), 30% ee; Fluka Grade $[\alpha]_D^{20}$ -45 $\pm$ 1, (*c* = 5 in MeOH), >99% pure (GC)].

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