Chiral Alcoholates in Asymmetric Synthesis

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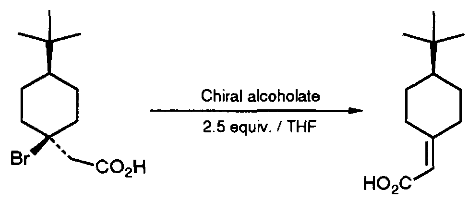
Enantioselective dehydrohalogenation reactions with enantiomeric excesses (e.e.) as high as 90% are promoted by chiral alcoholates as bases.

The usefulness of chiral lithium amides in asymmetric synthesis has been long known[1] and there are important applications of this class of reagents to enantioselective reactions.[2] Surprisingly, the literature does not provide, to the best of our knowledge, examples of asymmetric induction through the use of chiral alcoholates. We now report the first application of alcoholate acting as the chiral base in an enantioselective dehydrohalogenation reaction.

This first set of experiments has been carried out on prochiral brominated compound **1**, which leads upon treatment with a base, to axially dissymmetric acid **2** (Scheme 1).

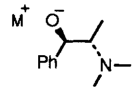
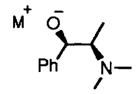


Prochiral **1**

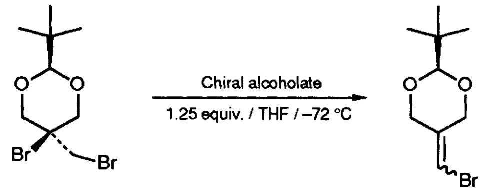
(*S*)-**2**

Scheme 1

Table 1

Entry	Chiral base	M+	$T/°C$	Yield (%)[a]	e.e. (conf.)[b]
1 2		Na^+ K^+	−72 −72	71 75	68 (*S*) 65 (*S*)
3 4 5		Na^+ K^+ K^+	−72 −72 −90	65 80 70	46 (*S*) 84 (*S*) 90 (*S*)

[a] For experimental procedure.† [b] Determined by polarimetry[3] and NMR analysis in the presence of chiral shift reagent.[4]



Prochiral **3** Optically active **4**

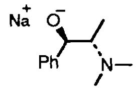
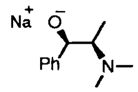
Scheme 2

Use of chiral alcoholates derived from *N*-methyl ephedrine or *N*-methyl pseudoephedrine gives access to optically active compounds as shown by results presented in Table 1.

Worthy of note is the result obtained in conditions described in entry 5, which demonstrates that this new class of chiral bases compares favourably with previously described chiral lithium amides.[4] A strong counterion effect may be observed in one case (entries 3 and 4).

These encouraging results prompted us to apply these same chiral bases to dibrominated prochiral compound **3** in an attempt to get optically enriched dioxane **4** (Scheme 2). This reaction, not described to date in the literature, leads to a comparable e.e. of about 55% with both *N*-methyl ephedrine and *N*-methyl pseudoephedrine sodium alcoholates at −72 °C (Table 2). The corresponding potassium alcoholates gave poor asymmetric induction (5 to 10% e.e.).

Table 2

Entry	Chiral base	$[\alpha]_D^{25}$[a]	e.e. (%)[b]	Yield (%)[c]
1		−17.5°	55	72
2		−15.5°	51	64

[a] c = 2, $CHCl_3$. [b] Determined by GPC (capillary column FS-HYDRODEX β-MT, 25 m × 0.25 mm ID, MACHEREY-NAGEL, carrier gas 0.6 bar He, split: 1 : 100; 150 °C; detection: FID 260 °C). [c] Synthesis and reactivity of compound **3** as well as full experimental procedure for dehydrohalogenation reaction will be published elsewhere.[5]

In conclusion, the preliminary use of chiral alcoholates as bases in two dehydrohalogenation reactions has led us to very promising results, and e.e. as high as 90% may be reached. *N*-Methyl ephedrine and *N*-methyl pseudoephedrine are cheap commercial materials, available in both enantiomeric forms and may easily be recovered upon workup.

We believe this new class of chiral bases to be promising tools for asymmetric synthesis; efforts are currently dedicated to extension and application of these findings.

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† In a typical experiment, the alcoholate was prepared by reaction of the metal hydride (2.5 mmol in 4 ml of THF) with the chiral alcohol (2.5 mmol in 2 ml of THF) for 20 min at reflux. The prochiral substrate **1** (1 mmol in 1 ml of THF) was added to the basic solution at −72 °C. The reaction mixture was left overnight at this temperature, then was quenched at −72 °C to give after usual work-up the chiral acid **2**, which was purified by flash chromatography (Silica gel GRACE AMICON 230-400 MESH, light petroleum : Et_2O = 90 : 10).

References

1 (*a*) L. Duhamel and J. C. Plaquevent, *Tetrahedron Lett.*, 1980, **21**, 2521; (*b*) J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 1980, **45**, 755.

2 For a review see, P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymm.*, 1991, **2**, 1.

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