Chiral Alcoholates in Asymmetric Synthesis: A Renewal in the Search for Chiral Bases

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Summary: Chiral alcoholates are efficient reagents to afford in optically pure form the cyclic acetal **1**, thus demonstrating the potential of this class of homochiral bases.

The use of chiral bases, such as chiral lithium amides, as efficient and versatile tools for asymmetric synthesis was introduced some years ago, simultaneously and independently by our group[1] and by Whitesell and Felman.[2] Whereas the potential of chiral lithium amides was extensively studied during the last decade,[3] chiral alcoholates were curiously put aside.

We wish to report here the first access to a new versatile chiron, using members of this class of chiral bases. Actually, the present study revealed chiral alcoholates to behave as efficient reagents to afford in optically pure form cyclic acetal **1** bearing a chiral axis, which is a chiron of great potential for asymmetric synthesis.[4]

The **2b** trans prochiral dibromide required for the asymmetric synthesis of chiron **1** was obtained in two steps from the ethylenic compound **3**. In the first step, stereospecific bromination of the ethylenic acetal **3** yielded exclusively the **2a** cis isomeric dibromide. Interestingly, we observed that the cis isomer **2a** was quantitatively isomerized into the trans isomer **2b** when submitted to hydrobromic acid vapors (Scheme 1).

Both stereoisomers **2a** and **2b** are crystalline solids; the stereochemistry indicated in Figure 1 was determined by single-crystal X-ray analysis.

When submitted to an excess of chiral alcoholate prepared from N,N-disubstituted norephedrine (Table 1),[5] compound **2b** led to chiron **1** through an enantioselective dehydrobromination. A single recrystallization of crude **1** provided the optically pure compound in 73% overall yield (Scheme 2). It is worth stressing that, in the special case of the reaction described herein, lithium amides failed to promote the dehydrohalogenation of compounds **2a** and **2b**.

The reaction involved the stereospecific removal of the *pro-R* proton, as indicated by the recovery of optically pure compound (*R*)-**1**. A strong counterion effect was observed (Table 1). In the case of **2b**, potassium alcoholates led to higher stereoselectivities than the corresponding sodium alcoholates, whereas a reverse counterion effect has been previously observed for the enantioselective dehydrohalogenation of the isomeric cis prochiral acetal **2a** bearing the bromine in the axial position.[6]

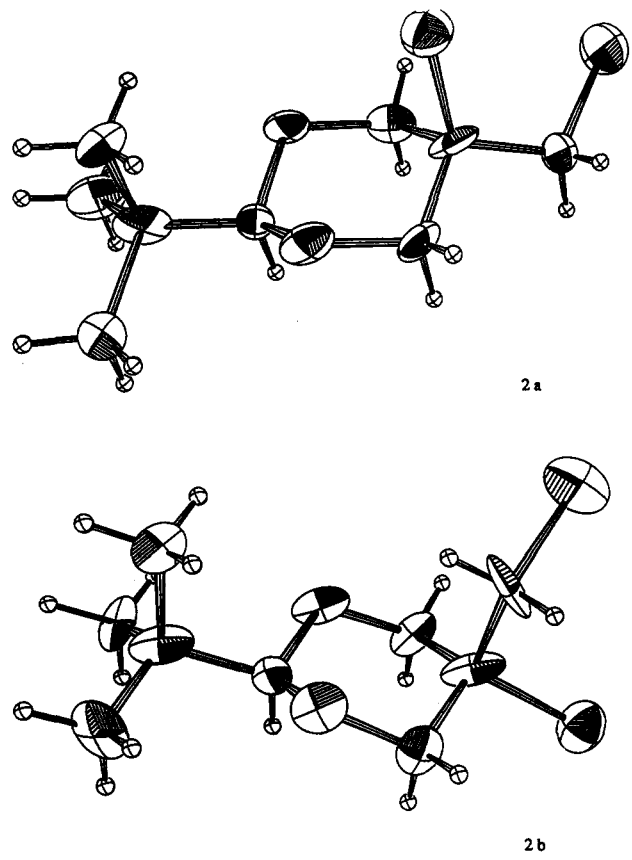
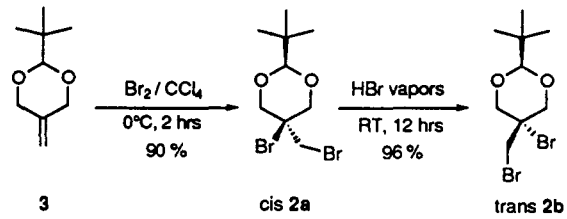


Figure 1. X-ray analysis of compounds **2a** and **2b**.

Scheme 1



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(1) Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1980**, *21*, 2521–2524.

(2) Whitesell, J. K.; Felman, S.W. *J. Org. Chem.* **1980**, *45*, 755–758.

(3) (a) For a review of asymmetric induction through the use of chiral lithium amides see: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymm.* **1991**, *2*, 1–26. (b) For enantioselective dehydrohalogenation reactions through the use of chiral lithium amides, see: Duhamel, L.; Ravard, A.; Plaquevent, J. C.; Plé, G.; Davoust, D. *Bull. Soc. Chim. Fr.* **1990**, *127*, 787–797 and references cited therein.

(4) For the use of acetals in synthesis see, for example: (a) Frauenrath, H. *Synthesis* **1989**, 721–734. (b) Enders, D.; Bockstiegel, B. *Synthesis* **1989**, 493–496. (c) Seebach, D.; Lapierre, J. M.; Jaworek, W.; Seiler, P. *Helv. Chim. Acta* **1993**, *76*, 459–475.

(5) Prepared according to: Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264–4268.

(6) Vadecard, J.; Plaquevent, J. C.; Duhamel, L.; Duhamel, P. *J. Chem. Soc., Chem. Commun.* **1993**, 116–117.

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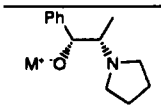
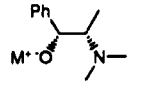
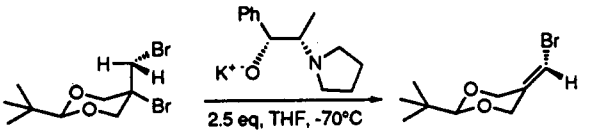
Table 1. Enantioselective Dehydrobromination of 2b by Means of Chiral Alcoholates Leading to Chiron (*R*)-1

chiral base	M^+	$[\alpha]^{25}_D$[a] (*R*)-1	ee[b] (%) (*R*)-1	yield (%) (*R*)-1
	Na^+		69	
	K^+	−31.9[c]	93[c]	60[c]
	K^+	−34.6[d]	>99[d]	73[d]
	Na^+		63	
	K^+	−30.5[c]	90[c]	68[c]
	K^+	−34.4[d]	>99[d]	72[d]

[a] c = 2, $CHCl_3$. [b] Determined by GPC (capillary column FS-Hydrodex β-MT, 25-m × 0.25-mm i.d., Macherey-Nagel, carrier gas 0.6 bar He, split, 1/100, 150 °C, detection FID 260 °C. [c] After flash chromatography of the crude material. [d] After one recrystallization of the crude material (from a saturated pentane solution).

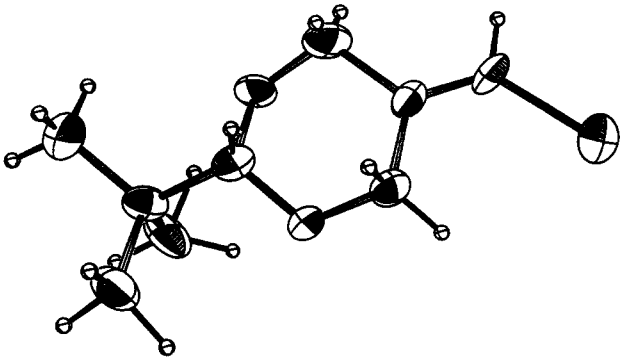
Scheme 2



trans 2b (R)-1

Recrystallized material: Yd: 73 %
ee > 99 %

The (*R*) configuration of the axially dissymmetric acetal 1 has been assigned by X-ray analysis of the optically pure sample (Figure 2).



(R)-1

Figure 2. X-ray analysis of compound (*R*)-1.

This first example of obtention of an optically pure compound (chiron 1) through the use of chiral alcoholates demonstrates their potential as chiral bases. Studies are in progress to generalize the application of chiral alcoholates and to apply chiron 1 to the synthesis of chiral compounds.[7]

Supplementary Material Available: Experimental procedure and spectral data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Amadji, M.; Vadecard, J.; Plaquevent, J. C.; Duhamel, L.; Duhamel, P. Unpublished results.