First Catalytic Enantioselective Proton Abstraction Using Chiral Alkoxides

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The present work discloses the first reported use of chiral alkoxides acting as chiral bases in a catalytic enantioselective proton abstraction; the chosen model reaction leads to enantiomerically enriched chirons **2** from prochiral dibromo acetals **1** through a highly enantioselective dehydrohalogenation reaction. A relay system allows the controlled regeneration of an achiral alkoxide (MeOK) and of a chiral one (potassium *N*-methylephedrinate **3(K)**).

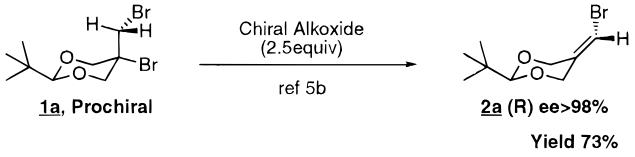
Asymmetric reactions under the influence of chiral bases have been the focus of intense research during the last decade. The first successful approaches were independently disclosed in 1980 by Whitesell and Felman[1] and by our group.[2] Since this date, numerous asymmetric reactions using chiral lithium amides have been described by us[3] and others[4] thus demonstrating the high potency of these chiral auxiliaries, able either to discriminate two enantiotopic protons of a prochiral substrate or to render enantioselective the addition of an electrophilic reagent to a prochiral nucleophilic intermediate generated by the chiral base. Catalytic versions have also been reported.[4g,h] As part of our study of chiral bases, we have recently focused on chiral alkoxides. Thus, we described highly enantioselective dehydrobromination reactions leading to axially dissymmetric compounds[5] (ee up to 98%). Nevertheless, these experiments required the use of an excess of the chiral potassium alkoxide (Scheme 1).

In order to achieve this reaction under *catalytic* conditions, the key problem was to design a system consisting of an achiral base (in excess) and of the chiral alkoxide (in catalytic amount) in which the achiral component would be able to deprotonate the chiral alcohol *but not* the prochiral substrate **1**.

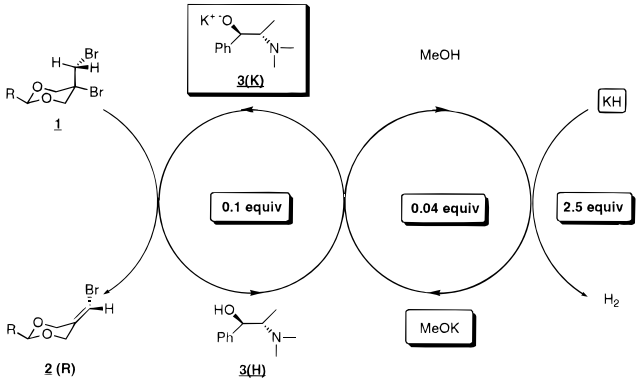
The reaction was carried out using the following components: (i) potassium hydride (excess); (ii) methanol (catalytic amount); (iii) *N*-methylephedrine (**3(H)**) (catalytic amount).

Indeed, KH was able to generate potassium methylate *in situ* at low temperature, and the resulting achiral alkoxide entered in equilibrium with the required potassium ephedrinate **3(K)**.

Scheme 1



Scheme 2



R = nPr, iPr, tBu, 65<ee(%)<90
R = Ph, $pPhC_6H_4$, $pO_2NC_6H_4$, $pMeOC_6H_4$, 94<ee(%)<99

Table 1. Catalytic Enantioselective Dehydrohalogenation of **1a**−**g** with **3(K)** as Chiral Alkoxide

run[a]	MeOH (equiv)		R		yield (%)	ee (%)[b]
1	0.4	**1a**	tBu	**2a**	not determined	68[c] (90)
2	0.2				not determined	83[c] (90)
3	0.05				not determined	86[c] (90)
4	0.04				83	90[c] (90)
					75[d]	>98[c,d] (>98)[d]
5	0.04	**1b**	nPr	**2b**	78	77[c] (79)
6	0.04	**1c**	iPr	**2c**	79	65[c] (65)
7	0.04	**1d**	$pPhC_6H_4$	**2d**	81	96[e] (>98)
8	0.04	**1e**	$pO_2NC_6H_4$	**2e**	78	>98[e] (>98)
9	0.04	**1f**	Ph	**2f**	82	94[e] (>98)
10	0.04	**1g**	$pMeOC_6H_4$	**2g**	79	>98[e] (>98)

[a] Reaction time: 72 h. Temperature: −80 °C. Experimental procedure for runs 4−10 is described in ref 8 (KH/MeOH/**3(H)**/**1** = 2.5:0.04:0.1:1). [b] In parentheses, ee obtained using 2.5 equiv of **3(K)** instead of the catalytic system. (*R*)-Configuration was assigned to **2a** and **2d** according to X-ray analysis (ref 5b, 7). [c] Determined by GC (see ref 8). [d] After one crystallization of the sample of entry 4. [e] Determined by HPLC (see ref 8).

This last reagent gave the expected asymmetric induction in the dehydrohalogenation of dibromo acetals **1**[6] (Scheme 2, Table 1).

Entries 1−4 show the influence of methanol concentration in the catalytic generation of the chiral alkoxide. The best result for **1a** (run 4 of Table 1, 90% ee, enhanced to 98% by crystallization) was obtained when using only 0.04 equiv of the achiral alcohol. This result compares with the similar reaction carried out with an excess of chiral alkoxide.[5b] In entries 5−10 are recorded results obtained using the best catalytic system (KH/MeOH/**3(H)** 2.5:0.04:0.1 equiv) for the enantioselective dehydrobromination[8] of **1** having several different substituents R. High enantioselectivities were obtained for aromatic derivatives **2d**−**g** (94−99% ee, without any crystallization), thus giving access to a variety of chirons in the 1,3-dioxane series.

We are currently evaluating the potential of these chirons for further studies in asymmetric synthesis and for the construc-

(1) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755−758.
(2) Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1980**, *21*, 2521−2524.
(3) (a) Duhamel, L.; Plaquevent, J. C. *Bull. Soc. Chim. Fr.* **1982**, (II), 75−83. (b) Duhamel, L.; Fouquay, S.; Plaquevent, J. C. *Tetrahedron Lett.* **1986**, *27*, 4975−4978. (c) Duhamel, L.; Ravard, A.; Plaquevent, J. C.; Davoust, D. *Tetrahedron Lett.* **1987**, *28*, 5517−5520. (d) Duhamel, L.; Duhamel, P.; Fouquay, S.; Jamal Eddine, J.; Peschard, O.; Plaquevent, J. C.; Ravard, A.; Solliard, R.; Valnot, J. Y.; Vincens, H. *Tetrahedron* **1988**, *44*, 5495−5506. (e) Duhamel, L.; Ravard, A.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **1990**, *1*, 347−350. (f) Duhamel, L.; Ravard, A.; Plaquevent, J. C.; Plé, G.; Davoust, D. *Bull. Soc. Chim. Fr.* **1990**, *127*, 787−797.
(4) For reviews (stoechiometric conditions), see: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1−26. (b) Simpkins, N. S. *Chem. Ind.* **1988**, 387−389. (c) Koga, K. *Yuki Gosei Kagaku Kyokaishi* **1990**, 463−475. (d) Waldmann, H. *Nachr. Chem. Tech. Lab.* **1991**, *39*, 413−418. (e) Reed, F. *Spec. Chem.* **1991**, *11*, 148−151. (f) Koga, K. In *New Aspects of Organic Chemistry II;* Yoshida, Z., Ohshiro, Y., Eds.; Kodansha: Tokyo, 1992; Chapter 5, pp 67−86. (g) Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793−796. (h) Koga, K.; Shindo, M. *J. Synth. Org. Chem. Jpn* **1995**, *53*, 1021−1032.
(5) (a) Vadecard, J.; Plaquevent, J. C.; Duhamel, L.; Duhamel P. *J. Chem. Soc., Chem. Commun.* **1993**, 116−117. (b) Vadecard, J.; Plaquevent, J. C.; Duhamel, L.; Duhamel, P.; Toupet, L. *J. Org. Chem.* **1994**, *59*, 2285−2286.
(6) Prochiral dibrominated dioxanes **1** were prepared according to the following: Amadji, M.; Vadecard, J.; Schimmel, U.; Plé, G.; Plaquevent, J. C. *J. Chem. Res., Synop.* **1995**, 362−363.
(7) Vadecard, J. Thesis, University of Rouen, France, 1994.

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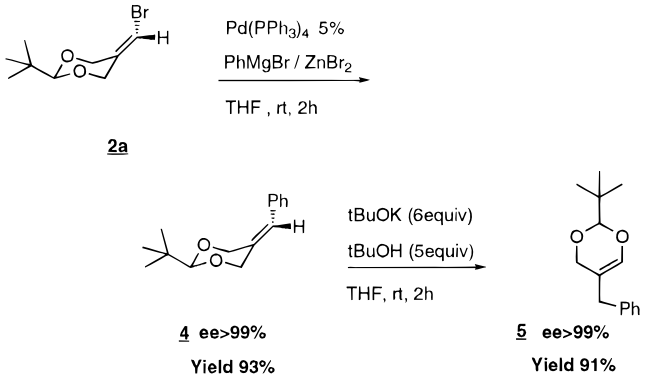
Scheme 3

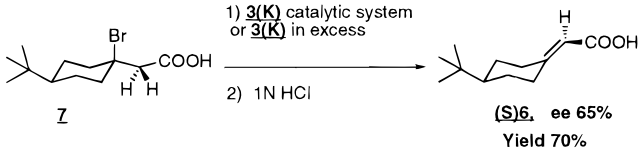


tion of chiral compounds.[9] For example, we have already prepared compounds **4** and **5** by the methodology described in Scheme 3, without loss of enantiomeric purity.

(8) The general experimental procedure is as follows. To a suspension of potassium hydride (2.5 mmol) in THF (8 mL) was added under argon atmosphere a solution of methanol (0.04 mmol) in THF (0.4 mL) at room temperature. After cooling at −80 °C, a solution of compound **1** (1 mmol) and of (1*R*,2*S*)-*N*-methylephedrine **3(H)** (0.1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was kept at −80 °C for 3 days. The workup and purification procedure for compounds **2a**−**e** was as follows: the reaction was quenched at −80 °C by aqueous 1 N hydrochloric acid (5 mL). Diethyl ether (5 mL) was then added, and the reaction mixture was allowed to warm to room temperature. After washing three times with aqueous 1 N hydrochloric acid, the resulting organic solution was neutralized by an aqueous saturated solution of sodium hydrogen carbonate and then dried over magnesium sulfate. After removal of the solvents, the crude material was chromatographed on silica gel 60 (petroleum ether/diethyl ether = 90:10 for compounds **2a**−**c**; petroleum ether/ethyl acetate = 90:10 for compounds **2d,e**). The workup and purification procedure for compounds **2f,g** was identical except that the use of hydrochloric acid was avoided and that all of the washings were an aqueous saturated solution of sodium hydrogen carbonate. The crude material was chromatographed on silica gel 60 using petroleum ether/ethyl acetate = 90:10 as eluent. The ee values of compounds **2a**−**c** were determined by GC (Supelco *β*-dex-120). The ee values of compounds **2d**−**g** were determined by HPLC (Chiracel OJ, isopropanol/hexane = 40:60, flow rate = 1 mL/mn).

(9) Amadji, M. Thesis, University of Rouen, France, in preparation. Also, unpublished results from our group.

Scheme 4



Finally, the use of the same catalytic system (**3(K)** as chiral alkoxide) was extended to the asymmetric synthesis of the axially dissymmetric acid **6**, giving similar results compared to those using the chiral base in excess[5a] (ee about 65%) (Scheme 4).

In conclusion, we have found an unprecedented catalytic system for enantioselective proton abstraction by means of chiral alkoxides. This finding reinforces the potential of chiral alkoxides,[10] chiral bases that are complementary to the better known chiral lithium amides. Finally, the methodology described herein allows the practical synthesis of useful chiral 1,3-dioxanes.[11]

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Supporting Information Available: Spectral and characterization details (3 pages). See any current masthead page for ordering and Internet access instructions.

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(10) Since the first communication from our group regarding the use of chiral alkoxides in enantioselective dehydrobromination reactions,[5a] some reports have been published on enantioselective deprotonation of meso epoxides (mixed amide−alkoxide bases), see: (a) Milne, D.; Murphy, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 884−885. (b) Hodgson, D. M.; Whitherington, J.; Moloney, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 337−338. (c) Hodgson, D. M.; Whitherington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3373−3377. (d) Hodgson, D. M.; Gibbs, A. M. *Tetrahedron: Asymmetry* **1996**, *7*, 407−408.

(11) For the use of cyclic acetals in synthesis, see: (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* **1991**, *56*, 4264−4268.