Enantioselective Dehydrohalogenation Using Chiral Alkoxides: Design of a Catalytic System Allowing Access to Axially Dissymmetric Compounds

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Received April 7, 1998

The use of chiral alkoxides obtained from ephedrines for enantioselective proton abstraction is described in full. These reagents allow the practical obtention of axially dissymmetric 1,3-dioxanes via highly enantioselective dehydrohalogenation reactions. The conditions for a catalytic use of these chiral alkoxides are defined.

Introduction

Asymmetric reactions under the influence of chiral bases have been the focus of intense research during the past decade. The first successful approaches were disclosed in 1980, simultaneously and independently 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, which are able either to discriminate two enantiotopic protons of a prochiral substrate (as well as the two enantiomers of a racemic pair) or to render enantioselective the addition of an electrophilic reagent to a prochiral nucleophilic intermediate generated by the chiral base. As part of our program on the study of chiral bases, we recently embarked on research directed toward a complementary class of basic auxiliaries, that is, chiral alkoxides. The aim of the study was to develop a new set of chiral bases that would be superior to lithium amides in some aspects (ease of preparation and handling, for example) and for which the literature does not provide examples of asymmetric induction through their use as Brönsted bases. In our previous communications,[5] we demonstrated that chiral alkoxides may be used as efficient and versatile tools for preparing enantiomerically pure chirons[6] bearing a chiral axis via highly enantioselective dehydrohalogenation reactions. We present herein synthetic and mechanistic details for the design of the required alkoxides and we disclose access to the catalytic version of the reactions studied.[7]

Results

We studied the enantioselective preparation of the chirons **3** starting from the prochiral dibrominated dioxanes *cis*- and *trans*-**1** (Scheme 1).

Access to the Prochiral Precursors. The synthesis and full spectral data regarding the prochiral precursors **1** have been described elsewhere.[8] The general procedure to prepare the requisite compounds involved a stereospecific bromination of the ethylenic acetal **2** yielding either the cis or the trans isomer, depending on various parameters among which the nature of the R residue played a central role. It was possible to isomerize quantitatively the cis dibrominated acetal into the thermodynamic trans isomer under the action of hydrobromic acid vapor (the indicated configurations were determined by high-field NMR−NOEDS and X-ray crystallography). We wish to emphasize the importance of having a method that furnishes both of the geometric isomers of the prochiral precursors **1** in good yield (Scheme 1).

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S0022-3263(98)00645-8 CCC: $15.00
Published on Web 07/10/1998

Scheme 1. Access to the Prochiral Precursors 1

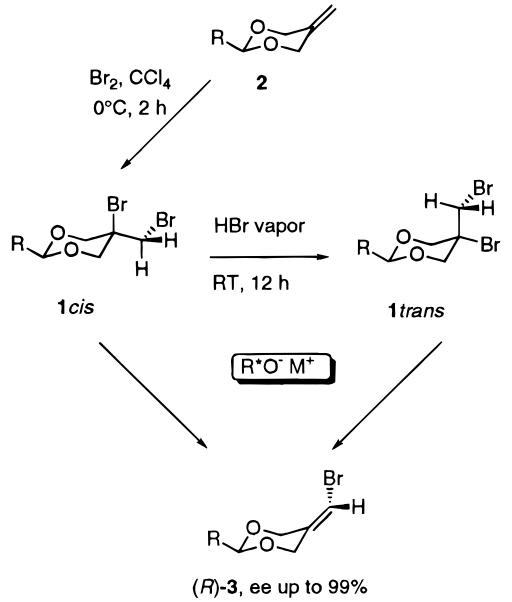

Table 1. Preliminary Attempts (from *cis*-1a, Sodium Alkoxides, 12 h, −70 °C to Room Temperature)

alcohol	**3a**, ee % (conf)
(*R*)-(−)-1-amino-2-propanol	2 (*S*)
(*S*)-(−)-2-amino-3-phenyl-1-propanol	3 (*R*)
(*S*)-(+)-2-amino-1-propanol	4 (*R*)
(*R*)-*S*-methyl cysteinol	2 (*R*)
(*S*)-(−)-1-methyl-2-pyrrolidinemethanol	6 (*R*)
[(*S*)-α,α′-diphenyl-*N*-methyl-2-pyrrolidinemethanol	0
(1*R*,2*R*)-(−)-*N*-methylpseudoephedrine	45 (*R*)
(1*R*,2*S*)-(−)-*N*-methylephedrine	51 (*R*)
(1*R*,2*S*)-(−)-ephedrine	42 (*R*)
(1*R*,2*S*)-(−)-norephedrine	35 (*R*)
(1*S*,2*S*)-(+)-2-amino-1- phenyl-1,3-propanediol	12 (*S*)
Chirald®	1 (*R*)

Enantioselective Dehydrobromination (Alkoxide in Excess). (a) Preliminary Attempts. To establish the efficiency of chiral alkoxides for inducing enantioselective reactions, we initiated a set of exploratory experiments in which we tested alkoxides derived from commercially available chiral alcohols. In each experiment, the prochiral substrate *cis*-**1a** (R = tBu) was added slowly to a solution of 2.5 equiv of the sodium alkoxide in THF at low temperature. After the usual workup, we recovered the expected chiral dioxane **3a** in fairly good yields (62−72%) and with ee values as high as 50% in some cases (Table 1).

The best enantioselectivities were achieved through the use of aminoalkoxides instead of "simple" alkoxides (menthol, borneol, 8-phenylmenthol, diacetonide-glucose, and 2,3-butanediol gave 0% < ee < 7%). On the other hand, it seemed that both the carbon atoms bearing the amino and the alcoholate groups had to be stereogenic in order to induce stereoselectivity (Table 1). In conclusion, ephedrine derivatives appeared to be the best candidates for further studies. This observation prompted us to continue the work by improving the structure of the chiral auxiliary derived from ephedrine and to try to optimize the experimental conditions for the reaction.

(b) Modification of the Nitrogen Substituents of Ephedrinates. We prepared a series of (1*R*,2*S*)-*N*,*N*-dialkylnorephedrines **4(H)** according to a procedure described in the literature (Figure 1);[9] we then submitted both dibrominated compounds *cis*-**1a** and *trans*-**1a** to chiral alkoxides derived from the corresponding amino alcohols. When carried out on the cis prochiral dioxane, the conversion into the axially dissymmetric compound **3a** was complete. In the other case (trans isomer), the reaction proceeded in various conversions (Table 2).

Figure 1. *N*,*N*-Dialkylnorephedrines and pseudonorephedrines.

Table 2. Modification of the Nitrogen Substituents of Ephedrinates (Sodium Alkoxides, 12 h, −70 °C to Room Temperature)

4(Na)		**3a**, from *cis*-**1a**[a]	**3a**, from *trans*-**1a**	
	NR_2	ee%[b,c]	conv %	ee%[b,c]
4a	NH_2	35	no reaction	no reaction
4b	NHMe	42	no reaction	no reaction
4c	$N(Me)_2$	51	73	63
4d	$N(Et)_2$	40	56	32
4e	$N(nPr)_2$	15	52	9
4f	$N(nBu)_2$	15	85	11
4g	$N(CH_2)_4$	54	100	69
4h	$N(CH_2)_5$	50	100	55

[a] Conversion (GC) is >99% in all cases. [b] All the products are of (*R*)-configuration. [c] See experimental part for column reference.

One of the plausible explanations may be a slower dehydrohalogenation rate in the latter case due to a less favorable configuration of the trans isomer (Scheme 1) in which the bromine atom to be removed is placed in an equatorial position. To improve the reactivity of the trans isomer, the use of stronger bases such as potassium alkoxides appeared worthwhile (see c).

In this series of experiments, we wish to point out that the enantioselectivity of the reaction is strongly dependent on both the configuration of the prochiral intermediate **1** and the nature of the nitrogen substituents. The best results were obtained starting from the trans isomer **1a** and using sodium alkoxides **4c(Na)** and **4g(Na)** bearing, respectively, the dimethylamino and the pyrrolidino moieties, which are the smallest dialkylamino groups (ee as high as 69%). We thus demonstrated the dramatic role of the steric hindrance of the nitrogen moiety of the base (see Table 2).

(c) Influence of the Counterion of the Alkoxide. To study the influence of the counterion, we prepared lithium, sodium (vide supra), and potassium alkoxides derived from **4c(H)** and **4g(H)**. Lithium alkoxides were hostilely discarded since they led to very poor conversion (<10%) of the prochiral compounds **1** into chiral dioxanes. In contrast to the sodium alkoxides, we observed that in the case of *cis*-**1a** (see Table 3), potassium alkoxides promoted a fast conversion of this prochiral dibromide at −70 °C. Unfortunatly, the strong counterion effect was accompanied by a dramatic decrease in enantioselectivity. The counterion effect was completely reversed when using the trans prochiral substrate **1a**: in this case, potassium alkoxides gave higher asymmetric induction than the corresponding sodium bases (ee as high as 90%,

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Table 3. Influence of the Counterion and of the Configuration of the Alkoxide

chiral alcoholate	**3a**, from *cis*-**1a**			**3a**, from *trans*-**1a**		
	conv %	yield %	ee %	conv %	yield %	ee %
4c(Na)[a]	100	72	51 (*R*)	73		63 (*R*)
4c(K)[b]	100	68	7 (*R*)	93	68	90 (*R*)
4g(Na)[a]	100	64	54 (*R*)	100		69 (*R*)
4g(K)[b]	100	65	9 (*R*)	94	60	93 (*R*)
Ψ4c(Na)[a]				77		4 (*R*)
Ψ4c(K)[b]				80		30 (*S*)

[a] 2.5 equiv of alkoxide, 12 h, −70 °C to room temperature. [b] 1.25 equiv of alkoxide, 2 h for *cis*-**1a**; 12 h for *trans*-**1a**, −**70** °C.

Table 4. Variation of the Structure of the Prochiral Dioxane *trans*-1 (Using 4c(K), 2.5 equiv, 12 h, −70 °C)

R		ee%[a,b]	yield %[b]
tBu	**3a**	90	68
		98[c]	72[c]
nPr	**3b**	79	73
p-PhC_6H_4	**3d**	>98	86
p-$O_2NC_6H_4$	**3e**	>98	82
Ph	**3f**	>98	85
p-$MeOC_6H_4$	**3g**	>98	81

[a] **3a**−**c**: determined by GC. **3d**−**g**: determined by HPLC. [b] After flash chromatography of the crude material. [c] After one crystallization of the crude material.

which can be improved to >98% by a single crystallization of **3a**). Moreover, the reaction times required at −70 °C for a complete transformation of the substrate *trans*-**1a** were longer (12 h) than for the cis isomer (2 h). This observation confirmed our previous hypotheses about the reactivity of the prochiral dibrominated compounds toward the sodium and potassium alkoxides (vide supra).

(d) Influence of the Configuration of the Alkoxide. In the same series of studies, we examined the influence of the alkoxide configuration on the enantioselective dehydrobromination of *trans*-**1a**. We noted a large effect of the configuration of the stereogenic center bearing the nitrogen atom of the ephedrine structure. Pseudoephedrine derivatives gave lower enantioselectivities when using both sodium and potassium counterions. In the latter case, the decrease in asymmetric induction was accompanied by an inversion of the absolute configuration of the recovered chiral dioxane (Table 3).

(e) Generalization of the Results (Variation of the Structure of the Dioxane). The excellent results summarized in the previous paragraphs prompted us to extend the methodology to other compounds (**3**) bearing different R residues in the acetalic position. Using the optimal experimental conditions determined above, axially chiral dioxanes **3** were obtained in high ee after purification by flash chromatography (Table 4).

Interestingly, examination of the results pointed out a large effect of the R residue on the extent of asymmetric induction: better results were obtained when R was an aryl group (ee > 98% for all the tested compounds). Nevertheless, we did not observe any significant influence of the electronic effect induced by substituents of the aryl moiety. On the other hand, ee values were slightly lower in the alkyl series.

The (*R*)-configuration of the compounds was assigned by X-ray analyses of single crystals of derivatives **3a** and **3d**.[5b,7]

(f) Miscellaneous Experiments. The modification of various physical parameters did not result in any improvement in the asymmetric dehydrohalogenation reaction (**4c(K)** as base, *trans*-**1a** as prochiral substrate). We observed that the best results were obtained at low temperature (−70 °C) with a fairly good linearity of the relation log(ee) = $f(T)$. Variations of the alkoxide concentration (0.21−0.021 M) and the number of equivalents used (1.25−5 equiv) did not provide any significant improvement in the enantiomeric excesses. However, we noted that the use of an excess of alkoxide facilitated quantitative conversion of the *trans*-**1a** dibromide at low temperature.

Table 5. Enantioselective Dehydrohalogenation of *trans*-1d with Potassium Alkoxides Derived from *Cinchona* Alkaloids (2.5 equiv, 12 h, −70 °C)

amino alcohol	ee%	conf	yield %
quinine	25	*S*	85
cinchonidine	26	*S*	84
quinidine	19	*R*	80
cinchonine	19	*R*	76
N-methylephedrine	>98	*R*	86

In an attempt to rationalize the stereochemical outcome of the highly enantioselective dehydrohalogenation of the trans prochiral dibromides **1**, we compared the enantioselectivity of the reaction when carried out with more conformationally constrained aminoalkoxides. *Cinchona* alkaloids were elected for comparing with *Ephedra* alkaloids, using *trans*-**1d** as prochiral substrate (Table 5).

The lower ee values (Table 5) obtained confirmed our previous observation of the unfavorable influence of the steric hindrance at the near proximity of the nitrogen atom of the aminoalkoxide (see Table 2 regarding sodium alkoxides); these results also suggested that the actual reactive conformer of dialkylnorephedrinates **4(K)** could be different from the one in the *Cinchona* series.

In conclusion, we have described highly enantioselective dehydrobromination reactions leading to axially dissymmetric compounds (ee typically from 90 to 99%). Nevertheless, these experiments required the use of an excess of the chiral potassium alkoxide; the following section will describe our successful approach to a catalytic version of these enantioselective reactions.

Catalytic Use of Chiral Alkoxides. In this section, we wish to report our efforts to achieve a similar reaction carried out under *catalytic* conditions. The present work discloses the first reported use of chiral alkoxides acting as chiral bases in a catalytic enantioselective proton abstraction; the key problem was to design a system consisting of an achiral base (in excess) and the chiral alkoxide (in a substoichiometric amount) in which the achiral component would be able to deprotonate the chiral alcohol *but not* the prochiral substrate **1**. Our first approach was based on our observation that potassium hydride does not promote any significant dehydrohalogenation reaction on the starting material. Thus we treated the prochiral dibrominated compound *trans*-**1a** under various conditions (Scheme 2) using an excess of an achiral base (2.5 equiv) and a substoichiometric amount of *N*-methylephedrine **4c(H)**.

Results using KH as achiral base are reported in Table 6: at −70 °C, no reaction occurred when a substoichiometric amount of **4c(H)** was used, while an excess of alkoxide **4c(K)** (2.5 equiv) led to the previous result (Table 6, entries 1 and 2). This showed that, at −70 °C, potassium hydride does not react with either **1a** or with

Scheme 2. First and Second Catalytic Systems

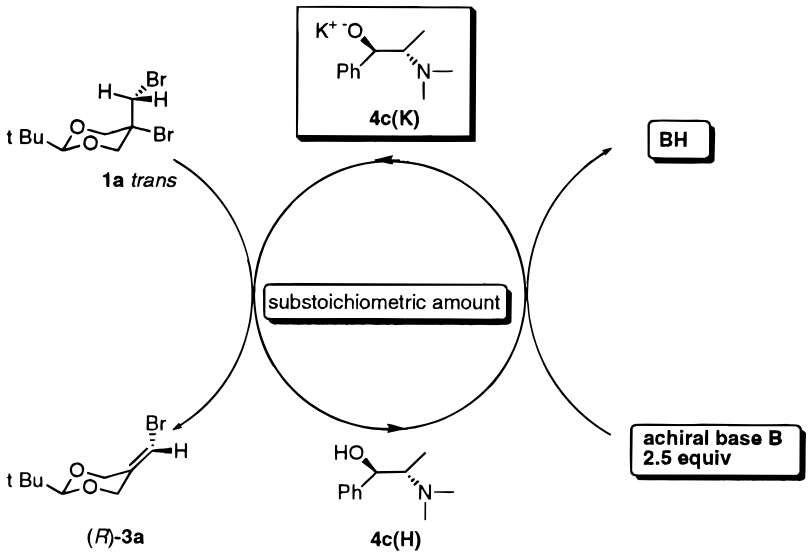


Table 6. Catalytic Enantioselective Dehydrohalogenation of *trans*-1a with 4c(K) [First System: KH as Achiral Base (Scheme 2)]

entry	nb equiv **4c(H)**[a]	time[b]	temp (°C)	ee %[c] **3a** (*R*)
1	2.5[d]	12 h	−70	90
2	0.25	12 h	$-70 < t < 20$	no reaction
3	2.5[d]	15 min	25	61
4	0.25	15 min	25	60
5	0.25	20 min	−17	68
6	0.05	90 min	−18	67

[a] KH/**1a** = 2.5/1. [b] Conversion >95% except for run 2. [c] Determined by GC. [d] In this experiment, **4c(K)** was previously prepared at rt from **4c(H)** and KH (2.5 equiv).

Table 7. Catalytic Enantioselective Dehydrohalogenation of *trans*-1a with 4C(K) [Second System: Alkoxides as Achiral Bases (Scheme 2)]

run	B[a]	time (h)	temp (°C)	conv %[b]	ee %[c] **3a** (*R*)
1	MeOK	72	−64	66	61
2	EtOK	72	−64	65	28
3	iPrOK	16	−78	60	11
4	tBuOK	16	−78	100	0

[a] Previously prepared from ROH and KH at room temperature (B/**4c(H)**/**1a** = 2.5/0.1/1). [b] Determined by GC. [c] Determined by GC and polarimetry.

4c(H). At room temperature (Table 6, entries 3 and 4), a complete reaction was observed either under catalytic conditions or with an excess of chiral alkoxide and, very interestingly, with identical stereoselectivity. Nevertheless, as expected, the enantioselectivity was lower than that obtained at low temperature. We also observed that the deprotonation of the alcohol function of **4c(H)** cannot be achieved with KH at a temperature lower than ca. −20 °C, and thus we performed the reaction at slightly higher temperature (Table 6, entries 5 and 6). The stereoselectivity was slightly higher than at room temperature. In entry 6, only 5% of chiral inductor **4c** was used, giving **3a** with an ee as high as 67%. Although encouraging, these results presented a major drawback: the unreactivity of potassium hydride as the deprotonating agent of **4c(H)** at very low temperature gives a modest asymmetric induction.

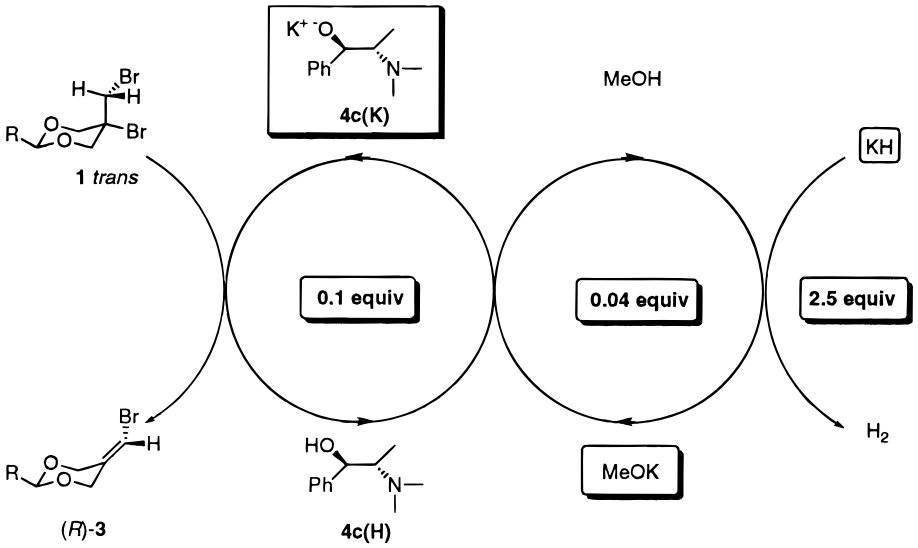
We then envisioned a second set of experiments in which another type of achiral base would be used, i.e., achiral potassium alkoxides. The aim was again to select a base able to deprotonate **4c(H)** at low temperature without reacting with *trans*-**1a** (Scheme 2 and Table 7).

From the results reported in Table 7, we note that in all cases a partial to total reaction was obtained. In addition, it is very interesting to observe that the enantioselectivity decreased when the basicity of the achiral alkoxide increased (from 61% ee with MeOK to 0% with tBuOK; Table 7, entries 1 to 4). This clearly indicated that the excess of achiral alkoxide promoted an unselective dehydrobromination reaction in competition with the enantioselective elimination by the in situ generated chiral base. The more basic the achiral alkoxide, the less selective the reaction, as one can expect. Nevertheless, we were delighted to be able to generate **4c(K)** at lower temperatures (−78 °C) in contrast to using KH as achiral component in the catalytic system. As previously outlined (vide supra), the drawback in this case was the ability of the excess of MeOK (Table 7, entry 1) to carry out part of the elimination reaction, thus lowering the asymmetric induction which was expected at low temperature. To design a powerful catalytic system (vide infra), we took into account all of this and carried out the reaction using the following components: (i) potassium hydride in excess, (ii) methanol in substoichiometric amount, and (iii) *N*-methylephedrine **4c(H)** in substoichiometric amount.

Indeed, KH was able to generate in situ potassium methylate at low temperature, and the resulting achiral alkoxide entered in equilibrium with the required potassium ephedrinate **4c(K)**; the latter reagent afforded the expected asymmetric induction in the dehydrohalogenation process of *trans*-**1a** (Scheme 3, Table 8, entries 1−4). The other prochiral substrates *trans*-**1** were then submitted to this procedure, all exhibiting a highly enantioselective reaction (Table 8).

In entries 1−4 we demonstrated the influence of the quantity of methanol used in the catalytic generation of the chiral alkoxide. The best result for **3a** (Table 8, entry 4, ee 90%) was obtained when using 0.04 equiv of the achiral alcohol. This result compares favorably with the corresponding reaction performed with an excess of chiral alkoxide (see previous part). Entries 5−10 record results obtained when using the best catalytic system [2.5 equiv

Scheme 3. Third Catalytic System



Scheme 4. Application to Cyclohexylidenic Derivative

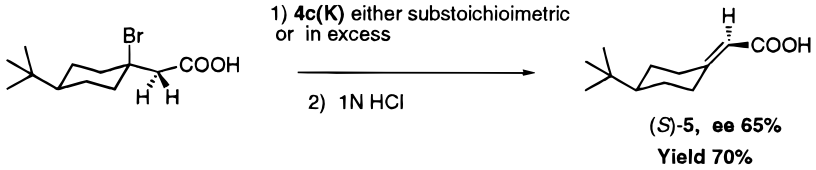


Table 8. Catalytic Enantioselective Dehydrohalogenation of *trans*-1a−g with 4c(K) as Chiral Alkoxide [Third System (Scheme 3)]

entry[a]	MeOH equiv		R		yield %[b,c]	ee %[c,d]
1	0.4	**1a**	tBu	**3a**	nd[f]	68 (90)
2	0.2	**1a**	tBu	**3a**	nd	83 (90)
3	0.05	**1a**	tBu	**3a**	nd	86 (90)
4	0.04	**1a**	tBu	**3a**	83 (68)	90 (90)
	0.04	**1a**	tBu	**3a**	75 (72)[e]	>98 (>98)[e]
5	0.04	**1b**	nPr	**3b**	78 (73)	77 (79)
6	0.04	**1c**	iPr	**3c**	79 (77)	65 (65)
7	0.04	**1d**	*p*-PhC_6H_4	**3d**	81 (86)	96(>98)
8	0.04	**1e**	*p*-$O_2NC_6H_4$	**3e**	78 (82)	>98 (>98)
9	0.04	**1f**	Ph	**3f**	82 (85)	94 (>98)
10	0.04	**1g**	*p*-$MeOC_6H_4$	**3g**	79 (81)	>98 (>98)

[a] Reaction time, 72 h; temperature, −80 °C (KH/MeOH/**4c(H)**/**1** = 2.5/0.04/0.1/1). [b] After chromatography. [c] In parentheses, values obtained using 2.5 equiv of **4c(K)** instead of the catalytic system. (*R*)-configuration was assigned to **3a** and **3d** according to X-ray analysis. [d] **3a**−**c**, determined by GC; **3d**−**g**, determined by HPLC. [e] After one crystallization of the sample in entry 4. [f] nd = not determined.

of KH/0.04 equiv of MeOH/0.1 equiv of **4c(H)**] for the enantioselective dehydrobromination of the other prochiral compounds *trans*-**1,** where we modified the nature of the R residue of the acetal moiety. Very high enantioselectivities were also obtained, especially for aromatic derivatives **3d**−**g** (ee from 94 to >98%), thus giving us access to a variety of chirons in the 1,3-dioxane series, which could be useful for further studies in asymmetric synthesis and for the construction of chiral compounds.[10]

In addition, the application of the same catalytic system [**4c(K)** as chiral alkoxide] was extended to the asymmetric synthesis of a carbocyclic substrate (axially dissymmetric acid **5**), this reaction giving similar results compared to those using the chiral base in excess[5a] (ee about 65%) (Scheme 4).

Conclusion

In conclusion, we have described an unprecedented catalytic system for enantioselective proton abstraction by means of chiral alkoxides. This finding seems remarkable since it reinforces the potential of the chiral alkoxides,[11] which compare favorably with the better known chiral lithium amides. Finally, the methodology described herein allows the practical formation of useful chiral 1,3-dioxanes.[12] Further studies on catalytically generated alkoxides are under investigation, including mechanistic aspects, as well as on the use of the chirons **3** in synthesis of chiral compounds.[10]

(10) Amadji, M.; Cahard, D.; Moriggi, J. D.; Toupet, L.; Plaquevent, J. C. *Tetrahedron: Asymmetry* **1998**, 1657−1660.

(11) 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. (e) Kumamoto, T.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 753−755.

(12) For the use of cyclic 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* **1991**, *56*, 4264−4268.

Experimental Section

The preparation and full description data for prochiral dibrominated compounds **1** have already been published.[8] The preparation of the *N*,*N*-dialkylnorephedrines **4(H)** was carried out according to literature methods.[9]

Typical Experiment (Catalytic Version). The general experimental procedure is as follows. To a suspension of potassium hydride (2.5 mmol) in THF (8 mL) was added under an argon atmosphere a solution of methanol (0.04 mmol) in THF (0.4 mL) at room temperature. After cooling to −80 °C, a solution of compound **1** (1 mmol) and of (1*R*,2*S*)-*N*-methylephedrine **4c(H)** (0.1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was kept at −80 °C for 4 days. The workup and purification procedure for compounds **3a**−**e** was as follows: the solution 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 by 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 volatiles, the crude material was chromatographed on silica gel 60 (petroleum ether/diethyl ether = 90/10 for compounds **3a**−**c**; petroleum ether/ethyl acetate = 90/10 for compounds **3d**−**e**). The workup and purification procedure for compounds **3f**−**g** was identical, except that the use of hydrochloric acid was avoided and that all the washings were carried out by means of an aqueous saturated solution of sodium hydrogencarbonate. The crude material was chromatographed on silica gel 60 using petroleum ether/ethyl acetate = 90/10 as eluent. The ee values of compounds **3a**−**c** were determined by GC (Supelco β-dex-120). The ee values of compounds **3d**−**g** were determined by HPLC (Chiracel OJ, 2-propanol/hexane = 40/60, flow = 1 mL/mn).

(*R*)-2-*tert*-Butyl-5-bromomethylidene-1,3-dioxane (3a). $[\alpha]^{20}_D = -34.6$ (1, $CHCl_3$), ee >98%; ^{1}H NMR (200 MHz, $CDCl_3$) 0.9 (s, 9H), 4.10(d, 1H, J = 14 Hz), 4.15 (s, 1H), 4.20 (d, 1H, J = 14 Hz), 4.40 (d, 1H, J = 14 Hz), 4.80 (d, 1H, J = 14 Hz), 6.10 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 24.6, 34.7, 67.5, 69.9, 102.1, 107.6, 135.3; IR (film, cm^{-1}) 1649; MS(CI, ^{i}BuH) *m*/*e*: 237, 235, 179, 177; mp 60 °C. Anal. Calcd for $C_9H_{15}BrO_2$: C, 45.98; H, 6.43. Found: C, 45.68; H, 6.78.

(*R*)-2-*n*-Propyl-5-bromomethylidene-1,3-dioxane (3b). $[\alpha]^{20}_D = -27.0$ (1, $CHCl_3$), ee 79%; ^{1}H NMR (200 MHz, $CDCl_3$) 0.88 (t, 3H, J = 7.2 Hz), 1.32−1.63 (m, 4H), 4.10 (d, 1H, J = 13.5 Hz), 4.18 (d, 1H, J = 13.5 Hz), 4.32 (d, 1H, J = 13.5 Hz), 4.59 (t, 1H, J = 5 Hz), 4.81 (d, 1H, J = 13.5 Hz), 6.10 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 13.8, 17.2, 36.5, 67.3, 69.8, 102.0, 102.6, 135.0; IR (film, cm^{-1}) 1644; MS (EI) *m*/*e* 222, 221, 220, 219, 179, 177. Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93. Found: C, 43.43; H, 5.80.

(*R*)-2-Isopropyl-5-bromomethylidene-1,3-dioxane (3c). $[\alpha]^{20}_D = -23.0$ (1, $CHCl_3$), ee 65%; ^{1}H NMR (200 MHz, $CDCl_3$) 0.81 (d, 6H, J = 6.9 Hz), 1.69−1.88 (m, 1H), 4.1 (d, 1H, J = 13.6 Hz), 4.13−4.39 (m, 3H), 4.79 (d, 1H, J = 13.6 Hz), 6.10 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 16.9, 32.4, 67.4, 69.9, 102.4, 105.7, 135.2; IR (film, cm^{-1}) 1644; MS (EI) *m*/*e* 222, 221, 220, 219, 179, 177. Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93. Found: C, 43.86; H, 6.13.

(*R*)-2-*p*-Diphenyl-5-bromomethylidene-1,3-dioxane (3d). $[\alpha]^{20}_D = -104$ (1, $CHCl_3$), ee >98%; ^{1}H NMR (200 MHz, $CDCl_3$) 4.40 (d, 1H, J = 14 Hz), 4.47 (d, 1H, J = 14 Hz), 4.57 (d, 1H, J = 14 Hz), 5.00 (d, 1H, J = 14 Hz), 5.66 (s, 1H), 6.23 (s, 1H), 7.25−7.65 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) 67.8, 70.3, 101.2, 103.3, 126.5, 127.1, 127.4, 128.7, 134.6, 136.4, 140.7, 142.0; IR (film, cm^{-1}) 1650; MS(EI) 332, 330, 181, 152; mp 134−135 °C. Anal. Calcd for $C_{17}H_{15}BrO_2$: C, 61.65; H, 4.56. Found: C, 61.63; H, 4.59.

(*R*)-2-*p*-nitrophenyl-5-bromomethylidene-1,3-dioxane (3e). $[\alpha]^{20}_D = -90.0$ (1, $CHCl_3$), ee >98%; ^{1}H NMR (200 MHz, $CDCl_3$) 4.38 (d, 1H, J = 13.5 Hz), 4.48 (d, 1H, J = 13.2 Hz), 4.57 (d, 1H, J = 13.2 Hz), 5.02 (d, 1H, J = 13.5 Hz), 5.68 (s, 1H), 6.26 (s, 1H), 7.65 (d, 2H, J = 8.5 Hz), 8.22 (d, 2H, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 67.8, 70.2, 99.6, 103.9, 123.4, 127.2, 133.9, 143.9, 148.2; IR (cm^{-1}) 1650; MS (EI) *m*/*e* 301, 300, 299, 298, 220; mp 144 °C. Anal. Calcd for $C_{11}H_{10}BrNO_4$: C, 44.02; H, 3.36; N, 4.67. Found: C, 44.02; H, 3.57; N, 4.51.

(*R*)-2-Phenyl-5-bromomethylidene-1,3-dioxane (3f). $[\alpha]^{20}_D = -119$ (1, $CHCl_3$), ee >98%; ^{1}H NMR (200 MHz, $CDCl_3$) 4.37 (d, 1H, J = 13.5 Hz), 4.44 (d, 1H, J = 13.5 Hz), 4.55 (d, 1H, J = 13.5 Hz), 5.00 (d, 1H, J = 13.5 Hz), 5.61 (s, 1H), 6.21 (s, 1H), 7.33−7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 67.8, 70.2, 101.4, 103.2, 126.0, 128.3, 129.1, 134.6, 137.4; IR (cm^{-1}) 1650; MS (EI) *m*/*e* 256, 255, 254, 253, 179, 177; mp 54 °C. Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.79; H, 4.35. Found: C, 51.51; H, 4.37.

(*R*)-2-*p*-methoxyphenyl-5-bromomethylidene-1,3-dioxane (3g). $[\alpha]^{20}_D = -121$ (1, $CHCl_3$), ee >98%; ^{1}H NMR (200 MHz, $CDCl_3$) 3.78 (s, 3H), 4.38 (d, 1H, J = 13.6 Hz), 4.43 (d, 1H, J = 13.6 Hz), 4.52 (d, 1H, J = 13.6 Hz), 4.99 (d, 1H, J = 13.6 Hz), 5.56 (s, 1H), 6.20 (s, 1H), 6.88 (d, 2H, J = 8.9 Hz), 7.39 (d, 2H, J = 8.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 55.2, 67.8, 70.2, 101.3, 103.1, 113.6, 127.3, 129.3, 134.6, 160.1; IR (cm^{-1}) 1650; MS (EI) *m*/*e* 286, 285, 284, 283, 205; mp 96 °C. Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60. Found: C, 50.96; H, 4.69.

Acknowledgment. The authors wish to thank the Conseil Régional de Haute-Normandie, for a research grant attributed to one of us (M.A.), and Dr. L. Toupet (University of Rennes, France), for the determination of crystal structures.

Supporting Information Available: Chromatographic analysis of compound **3** (1 page). 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.

JO9806456