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Kinetic resolution of racemic alkoxy oxiranes by chiral lithium amides

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Abstract

The isomerization of alkoxy oxiranes with chiral lithium amides has been carefully investigated with the aim of finding an enantioselective approach to hydroxy enolethers, a class of compounds which can be used for further synthetic elaborations.

1. Introduction

In the last few years we have carefully investigated the base-induced isomerization of alkoxy oxiranes to hydroxy vinyl ethers by means of mixed metal bases. We have shown that when disubstituted oxiranes **1** are treated with an equimolar mixture of butyllithium/diisopropylamine/potassium *tert*-butoxide (LIDAKOR[1–3]) a *syn*-periplanar β-elimination process takes place leading to the *Z*- or *E*-enolethers **2** depending on the configuration of the starting epoxide.[4,5] The *cis*-isomer gives the *E*-enolethers as the exclusively isomerized product while the *trans*-isomer leads to a 30:70 mixture of *Z*- and *E*-enolethers (Scheme 1).

Due to the importance of the hydroxy vinyl ethers as 'building blocks' for the synthesis of highly functionalized molecules, we planned to extend our studies to the kinetic resolution of racemic alkoxy oxiranes with chiral lithium bases. The aim of such an investigation is to access enantiomerically enriched (or pure) hydroxy vinyl ethers by a direct and simple method from racemic materials, thus complementing the other route via Sharpless[6,7] epoxidation of allylic alcohols followed by base promoted isomerization.[4] The latter method is presently far superior from a synthetic point of view but the kinetic resolution of

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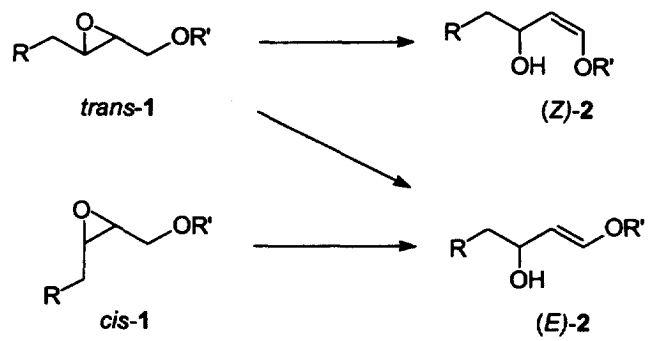


Scheme 1.

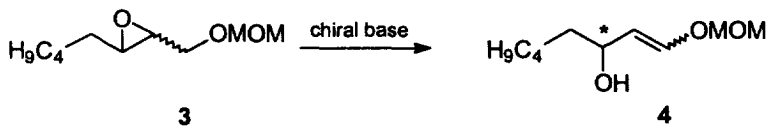
our racemic substrates can be of interest for further speculations. The use of chiral lithium bases in the enantioselective deprotonation of prochiral epoxides is well documented[8–15] but only a few reports have appeared concerning the kinetic resolution of racemic epoxides by a chiral lithium amide.[16]

The former area has been investigated since 1980 when Whitesell and Felman reported[17] the conversion of cyclohexene oxide to (*S*)-2-cyclohexen-1-ol in a 31% ee. It was later studied in detail by Asami[18–20] and Singh[9] who were able to achieve up to 92% ee for the same reactions using (*S*)-proline-based bases. A variety of symmetric epoxides and homochiral lithium amides have been employed for this transformation[8,21] but much less is known about the kinetic resolution of unsymmetrically substituted epoxides.

In addition, homochiral lithium amides have been, in a few cases, used to generate optically active allylic alcohols from racemic epoxides via a kinetic resolution process.[16] In these reactions, a deficiency of chiral base is used in order to convert the fast reacting epoxide enantiomer into the allylic alcohol with ees which seldom exceed 60%.[22]

2. Results and discussion

The target of our present study is to find optimal conditions in order to convert a monocyclic heterosubstituted racemic epoxide **3** into an enantiomerically pure hydroxy vinyl ether **4** (Scheme 2).



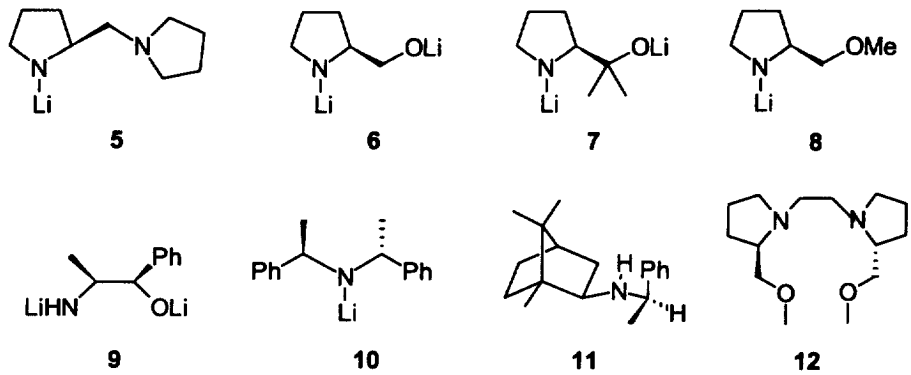
3 **4**

Scheme 2.

According to the observation by H.-J. Gais,[21] "finding the optimal chiral lithium amide and reaction parameters remains largely empirical". Guided by this statement we have undertaken a study on our target reactions examining a reasonable number of chiral bases and reaction conditions. Following literature reports on similar transformations, the lithium amides **5–11** have been used (Scheme 3).

The precursor amines of **5**, **6**, **8**, **9** and **10** are commercially available while amines **7**, **11** and **12** have been prepared following known procedures.[23,24] The proline derived bases **5–8**, in particular the lithium pyrrolidinyl pyrrolidine **5**, have been chosen for their known efficiency in promoting the isomerization of symmetrical oxiranes.

Amines **6**, **7** and **9** are characterized by the presence of a free hydroxyl group which is transformed into an alcoholate, thus allowing complexation during the isomerization reaction. The C_2-symmetrical lithium amide **10** and the hindered amide **11** have been chosen for some promising results reported in



5 6 7 8 9 10 11 12

Scheme 3.

similar studies. We have also prepared the C_2-symmetrical tertiary amine **12** which was used as a chiral ligand of *sec*-butyllithium in an isomerization reaction of *trans*-**3**.

Both the *cis*- and *trans*-2,3-epoxy-1-methoxymethoxyoctane **3** have been used in our investigation with 0.5 equivalents of the chiral lithium base.[22] Our results are shown in Tables 1 and 2 where we have reported the amine, the reaction conditions, the yields, the stereoselectivities and enantiomeric excesses as well as efficiency parameters S[25] and rate-constants ratios[22,26] for both stereoisomers. As a general remark, the *cis*-epoxide gives higher ees of the isomerized alkenol. Moreover, as already reported by us,[2] the *cis*-epoxide leads to the exclusive formation of the *E*-alkenol while the *trans*-epoxide always gives a mixture of *Z*- and *E*-isomerized products.

The best results (largest S values for both the *Z*- and the *E*-alkenols) with the *trans*-oxirane are obtained with the lithium pyrrolidinyl pyrrolidide **5** in benzene in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). In a similar way, both the *Z*- and *E*-alkenols are yielded in enantio-enriched form when **6** is used as the chiral base. However, the reaction in the presence of **9** in benzene (Table 1, entry 9) gives the largest rate-constant ratio for the *Z*-product, while the reaction with the lithium bis-(*R*)-1-phenylethyl amide **10** in pentane shows the largest rate-constant ratio for *E*-**4**.

The addition of potassium *tert*-butoxide to the lithium amide **5** increases the *E*-selectivity but decreases the ee whereas DBU seems very important[19] leading to both an increase in yield and enantioselectivity. Reasonable results are also obtained with the two proline-derived amides **6** and **7** in benzene and pentane respectively. In general, apolar solvents seem to work better than THF, probably due to their high propensity to favour close interactions between the oxirane and the lithium amides. A mixture of *Z*- and *E*-alkenols is usually obtained, with a slight preference for the latter except when the dilithium norephedrine **9** is employed, giving the *Z*-alkenol preferentially. It is clear that in order to have good *E*-stereocontrol, potassium *tert*-butoxide is required, while when it is absent, complexation of lithium by the methoxymethyl group may be responsible for a higher *Z*-preference. The reaction of *trans*-**3** with *sec*-butyllithium in the presence of the amine **12**, resulted in a 1:2 mixture of *Z*- and *E*-**4**, the latter isomer being partially (ee=20%) resolved.

When the *cis*-oxirane is used, the *E*-selectivity is noteworthy and even the enantiomeric excesses are higher for the forming *E*-alkenol than in the previous case. In particular, satisfactory results are again obtained with the lithium pyrrolidinyl pyrrolidide **5** in benzene/DBU, with the proline derived amide **6** in pentane and benzene and with the lithium bis-(*R*)-1-phenylethyl amide **10** in pentane. These experiments give the highest efficiency factors S, rate-constant ratios and ee values for the *E*-alkenol which is the unique recovered isomerized product. The reactions in the presence of **6** also demonstrate the crucial role of second order interactions (with the chiral ligands as well as with the solvent) in such a kinetic

Table 1
Isomerisation and kinetic resolution of *trans*-2,3-epoxy-1-methoxymethoxyoctane **3** in the presence of 0.5 equiv. of chiral lithium amides to *Z*- and *E*-3-hydroxy-1-methoxymethoxyoct-1-ene **4**

No.	Amine	Solvent (additive)	Conditions	Yield (%)	**4** *Z/E*	*Z*-**4** ee (%)	*E*-**4** ee (%)	S_Z[a]	S_E[a]	k_1/k_2[b] (*Z*-**4**)	k_1/k_2[b] (*E*-**4**)
1.	**5**	THF (KO^{t}Bu)	-70 °C, 12 h	20	5/95	14 (R)	4 (S)	0.00	0.02	1.33	1.09
2.	**5**	THF (DBU)	25 °C, 12 h	28	46/54	10(R)	18(S)	0.03	0.05	1.24	1.48
3.	**5**	benzene (DBU)	25 °C, 12 h	45	45/55	29(R)	30(S)	0.12	0.15	1.95	2.04
4.	**5**	benzene	25 °C, 12 h	15	54/46	20(R)	25(S)	0.03	0.03	1.53	1.70
5.	**6**	benzene	0 °C, 3 h	41	31/69	30(R)	21(S)	0.08	0.12	1.94	1.66
6.	**7**	pentane	25 °C, 3 h	41	32/68	20(R)	20(S)	0.05	0.11	1.54	1.61
7.	**7**	benzene	0 °C, 2 h	24	39/61	20(R)	14(S)	0.04	0.04	1.53	1.36
8.	**9**	THF	25 °C, 12 h	30	65/35	5(S)	16(S)	0.02	0.03	1.12	1.41
9.	**9**	benzene	25 °C, 5 h	39	73/27	40(R)	2(S)	0.23	0.00	2.71	1.04
10.	**10**	THF	25 °C, 12 h	25	56/44	2(S)	34(S)	0.01	0.07	1.04	2.12
11.	**10**	pentane	25 °C, 12 h	25	32/68	16(S)	33(R)	0.03	0.11	1.40	2.12
12.	**10**	benzene	25 °C, 12 h	20	23/77	8(S)	28(R)	0.01	0.09	1.18	1.87
13.	**11**	benzene	25 °C, 12 h	15	20/80	14(R)	14(R)	0.01	0.03	1.33	1.35
14.	**11**	THF (DBU)	25 °C, 12 h	28	47/53	16(S)	22(S)	0.04	0.07	1.41	1.62
15.	**11**	THF	25 °C, 12 h	11	60/40	4(S)	10(S)	0.01	0.01	1.09	1.23
16.	**12**	THF	-55 °C, 16h	39	33/67	0	22(S)	0.00	0.11	1.00	1.68

[a] The S values show the efficiency of the resolution calculated according to the literature definition[25,26].

[b] The configuration of the faster forming enantiomer (rate constant: k_1) is given in the ee columns. The rate constant ratio was calculated with the assumption that we are dealing with a second order irreversible process.

resolution process. A simple change of the solvent from pentane to benzene results in a change of the configuration of the faster forming product (Table 2, entries 2 and 3). With the amide **10**, experiments using different amounts of base have also been carried out. As expected, the ee with 0.25 equiv. is higher, while it decreases when 0.75 equiv. of base are used. The reactions in the presence of **9** in benzene and **10** in tetrahydrofuran yielded some small amount of (*R*)- and (*S*)-*Z*-**4** with low ees, respectively.

In order to explain the higher enantioselectivity encountered with the *cis*-oxirane, we have to look at

Table 2
Isomerisation and kinetic resolution of *cis*-2,3-epoxy-1-methoxymethoxyoctane **3** in the presence of 0.5 equiv. of chiral lithium amides to *Z*- and *E*-3-hydroxy-1-methoxymethoxyoct-1-ene **4**

No.	Amine	Solvent (additive)	Conditions	Yield (%)	**4** *Z/E*	*Z*-4 ee[c] (%)	*E*-4 ee (%)	S_E[d]	k_1/k_2[e] (*Z*-4)	k_1/k_2[e] (*E*-4)
1.	**5**	benzene (DBU)	25 °C, 20 h	25	2/98		43(S)	0.21		2.87
2.	**6**	pentane	-50 °C, 18h	50	2/98		36(S)	0.35		2.92
3.	**6**	benzene	0 °C, 18 h	45	2/98		32(R)	0.28		2.45
4.	**7**	pentane	-50 °C, 16 h	34	2/98		10 (R)	0.07		1.28
5.	**7**	benzene	0 °C, 20 h	47	2/98		12 (R)	0.11		1.40
6.	**8**	benzene	0 °C, 20 h	39	2/98		28 (S)	0.21		2.09
7.	**9**	benzene	25 °C, 20 h	10	10/90	8(R)	33(S)	0.06	1.17	2.05
8.	**10**	THF	25 °C, 20 h	10	5/95	7(S)	22(S)	0.04	1.15	1.60
9.	**10**	pentane	-50 °C, 20 h	49	2/98		36(S)	0.35		2.88
10.	**10**	benzene	25 °C, 20 h	26	2/98		32(S)	0.16		2.15
11.	**10**	pentane	-50 °C, 20 h[a]	55	2/98		20 (S)	0.22		1.84
12.	**10**	pentane	-50 °C, 20 h[b]	16	2/98		42 (S)	0.13		2.64

[a]Experiment with 0.75 equivalent of reagent.

[b]Experiment with 0.25 equivalent of reagent.

[c]The S values of the resolution of the *cis* isomer are close to zero.

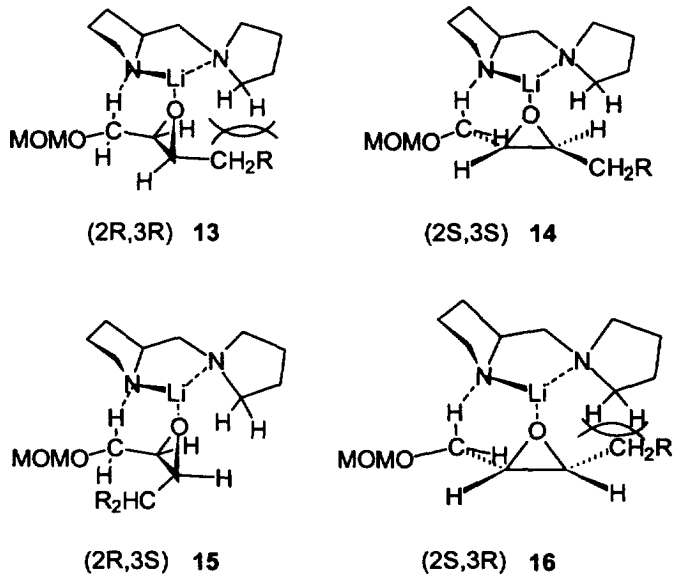
[d]The S values show the efficiency of the resolution calculated according to the literature definition[25,26].

[e]The configuration of the faster forming enantiomer (rate constant: k_1) is given in the ee columns.

the transition state for a *syn*-periplanar elimination reaction with the chiral lithium amides (the amide **5** as an example). The difference in steric interactions between transition states **13** and **14** relative to the *trans*-oxirane isomerization leading to the *E*-alkenol is lower than the same stability difference between the transition states **15** and **16** relative to the isomeriaztion of *cis*-oxirane to the *E*-alkenol. In both cases, the *S*-enantiomer is preferred as we have actually found (Scheme 4).

3. Experimental

Air and moisture sensitive compounds were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ether extracts were dried with sodium sulfate. Purifications by flash column chromatography[27] were performed using glass columns (10–50 mm wide); silica gel 230–400 mesh was chosen as the stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic



Scheme 4.

resonance spectra of hydrogen nuclei were recorded at 200 or 300 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Coupling constants (J) are measured in hertz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), m (multiplet), bs (broad singlet). Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). Mass spectra were obtained at a 70 eV ionization potential.

Anhydrous tetrahydrofuran and diethylether were distilled from sodium diphenylketyl. Pentane and benzene were distilled from sodium and stored over molecular sieves (4 Å). Petroleum ether, unless otherwise specified, was the 40–70°C boiling fraction. Diisopropylamine and all the prepared chiral amines were freshly distilled and stored under an argon atmosphere.

3.1. Preparation of substrates and amines

Both *cis*- and *trans*-2,3-epoxy-1-methoxymethoxyoctane **3** were prepared according to already reported procedures.[4] Amines **5**, **6**, **8**, **9** and **10** are commercially available, while amines **7**,[23] **11**[24] and **12**[28] were prepared following known methods.

3.2. Isomerization procedure with chiral lithium amides

The chiral amine (0.25 mmol) was dissolved in the solvent (0.7 mL) and cooled to 0°C. Then butyllithium was added (0.17 mL of a 1.6 M solution in hexane, 0.25 mmol; or double this amount as required for amines **6**, **7** and **9**) followed by the additive (0.25 mmol) after 30 minutes, if necessary. After stirring for 30 minutes at 0°C, the reaction mixture was taken to the specified temperature, and the epoxide (0.5 mmol) dissolved in the solvent (0.3 mL) was added and the mixture stirred for the required time. A saturated aqueous solution of NH_4Cl (1 mL) was then added to the mixture and the aqueous phase was extracted with ether (3×1 mL). The organic phase was washed with water (2 mL) and brine (2 mL), and dried. The crude mixtures were then analyzed either by GC (β-dex 120, β-cyclodextrins, 30 m length, 0.25 mm internal diameter, adsorbed on a polar phase SPB-35,

poly(35% diphenyl, 65% dimethyl)siloxane) or by ^{1}H-NMR (using the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] in deuterobenzene).

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