Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 2, pp. 399-402, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00017-1

Solvent Induced Isomerization of 2-Cyclohexen-1-ol to 3-Cyclohexen-1-ol by a Chiral Lithium Amide

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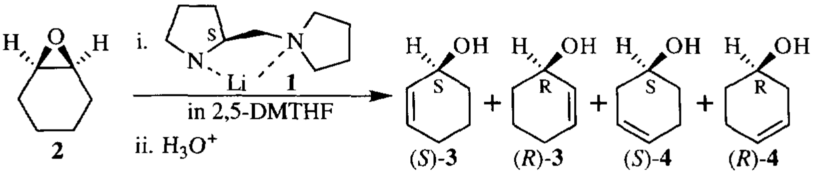
Abstract. Enantioselective deprotonation by lithium (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **1** of cyclohexene oxide **2** on changing the solvent from tetrahydrofuran (THF) to cis-2,5-dimethyl-THF (cis-DMTHF) gives the homoallylic alcohol 3-cyclohexen-1-ol **4** up to 74% yield as isomerized product besides the 2-cyclohexen-1-ol **3**. In the mixed solvent (THF/cis-DMTHF) **4** was isolated up to 51% yield (25% ee for (*S*)-**4**) and **3** in 42% yield (66% ee for (*S*)-**3**). In a separate experiment racemic **3** isomerized to racemic **4** in 74% yield when excess of **1** in DMTHF was used.

Recently special attention has been placed on the enantioselective deprotonation of a variety of epoxides to synthesize allylic alcohols in high yields and with high enantiomeric excess (ee).[1] A number of pheromones and drugs may be prepared starting from optically active allylic alcohols.[2]

Many chiral lithium amides have been designed[3] for enantioselective deprotonation of epoxides to 2-ene-1-ols. Thus lithium (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **1** enantioselectively deprotonates cyclohexene oxide **2** in THF to give 2-cyclohexene-1-ol **3** up to 78% yield (82% ee).[3a-d,4] The use of solvents other than THF have been found to have little or no effect in improving the yield or ee.[3b,5] Furthermore, no isomerization of allylic alcohols on the enantioselective deprotonation reaction of **2** with **1** seems to have been reported.[3a-3c, 5]

As a part of our studies of solvent effects[6,7] on lithiation reactions, we found a method to prepare homoallylic alcohol by further isomerization of the allylic alcohol. Here we wish to report our preliminary results.

Reaction of **1** with **2** in THF using the reported method[3a-b] gave **3** [Table 1, entry 1(a)] in 98% yield (80% ee). When the reaction was performed in DMTHF (52% cis and 48% trans) as solvent but under otherwise similar conditions, we observed the formation of 3-cyclohexen-1-ol **4** as identified by NMR spectroscopy and GC-MS (Scheme 1). The reactions were monitored by capillary gas chromatography on chiral stationary phases.[8] The exploratory experiments pointed toward the use of an excess of **1**.[9] Results from the experiments in different solvents are presented in Table 1.



Scheme 1

In DMTHF (52% cis and 48% trans), the reaction of **2** with **1** was followed to over 90% conversion (Table 1, entry 2). The yield of **4** was 64% (3 % ee for (*S*)-**4**) and that of **3** was 21% (24 % ee for (*S*)-**3**).

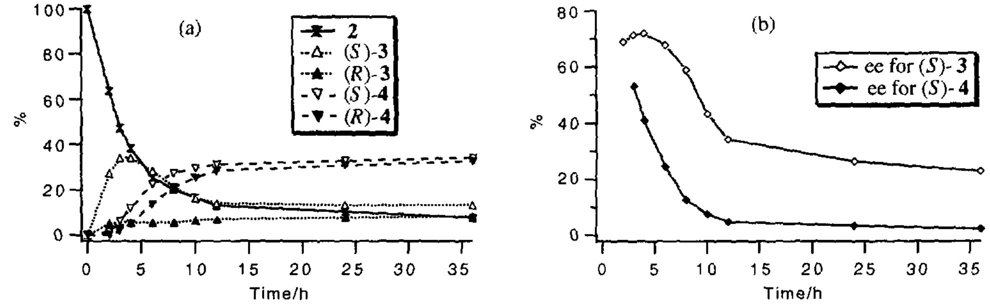
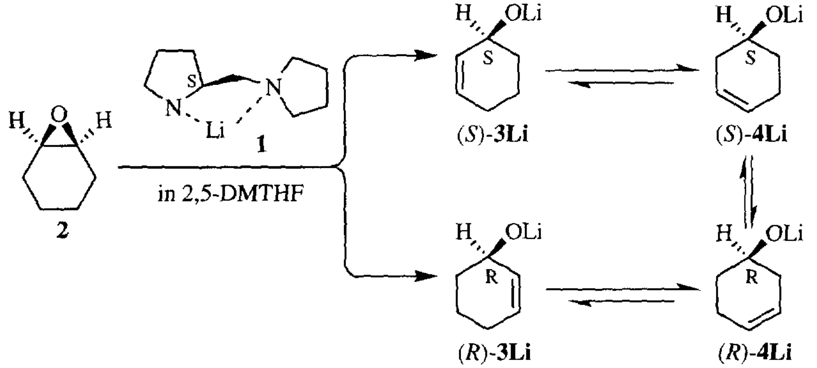


Figure 1. Variation of the percentage of (a) **2**, (*S*)-**3**, (*R*)-**3**, (*S*)-**4** and (*R*)-**4** and (b) ee for (*S*)-**3** and (*S*)-**4** during the reaction.

Figure 1 shows how the percentage of **2**, and enantiomers of **3** and **4** vary with time. Compound **4** is formed at the expense of **3**. Obviously the formation of (*S*)-**4** arises from the isomerization of the lithium alkoxide of (*S*)-**3**. The lithium alkoxide of (*S*)-**4** isomerizes to lithium alkoxide of (*R*)-**4** that may also be formed from lithium alkoxide of (*R*)-**3**. All the isomerizations of the alkoxides are reversible, as indicated in Scheme 2.



Scheme 2

In cis-DMTHF (99%)[10] **4** was obtained (Table 1, entry 3) after 24 hours in 68% yield (6% ee for (*S*)-**4**) and **3** in 21% yield (33% ee for (*S*)-**3**). The yield of **4** increased to 74% after 72 hours. When the reaction was performed in 5% THF in cis-DMTHF (v/v), the ee of **4** improved (Table 1, entry 6). At about 98% conversion, **4** was isolated in 51% yield (25% ee for (*S*)-**4**) along with **3** in 42% yield (66% ee for (*S*)-**3**) after 24 hours.

The use of 2,2,5,5-tetramethyl-THF (TMTHF) gave poor yields (Table 1, entry 9). In 2-methyl-THF (MTHF), less isomerization of **3** to **4** was observed. The use of trans-DMTHF or other mixtures of THF and DMTHF did only result in moderate changes in yields and ee:s.

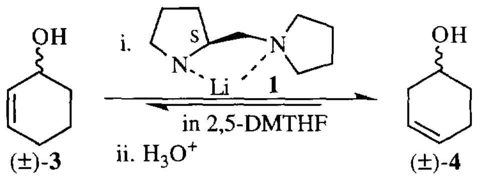
The results of the reactions in diethyl ether (DEE) and dimethoxyethane (DME) are in contradiction to results previously reported in the literature.[3b] However, those studies seem to have overlooked the formation of **4** along with **3** in the deprotonation of **2**.

In a separate experiment almost racemic **3** was mixed with 2.4 equivalents of *n*-BuLi in DMTHF. No product **4** was detected after 12 hours. Similarly a mixture of equivalent amounts of **3** and **1** did not result in any observable quantity of **4** in DMTHF. However, if more than two equivalent of **1** was used[11] the conversion of **3Li** to **4Li** took place (Scheme 3) and **4** was obtained in 74% yield (1% ee for (*S*)-**4**) and 13% of **3** was recovered. In cis-DMTHF **4** was obtained in 69% yield (4% ee for (*S*)-**4**) and 17% of **3** was recovered.

Table 1. Results of Enantioselective Deprotonation of Cyclohexen oxide **2** to 2-Cyclohexen-1-ol **3** and its Subsequent Isomerization to 3-Cyclohexen-1-ol **4** with **1**[a] in Different Solvents.

Entry	Solvent	Reaction time/h	% Conversion **2**[b]	**3**[c]		**4**[c]	
				yield/%	ee/%/(S)	yield/%	ee/%/(S)
1(a)	THF	24	98	98[d]	80[d]	0	0
1(b)	THF	48	99	89	70	0	0
2	DMTHF (52% cis and 48% trans)	10	83	23	43	55	8
		24	90	21	24	64	3
3	DMTHF (99% cis and 1% trans)	12	80	35	66	42	19
		24	92	21	33	68	6
		72	95	17	29	74	5
4	DMTHF (2% cis and 98% trans)	10	83	21	33	59	4
		20	92	21	13	68	3
		48	92	15	7	73	1
5	5% THF in DMTHF (v/v) (52% cis and 48% trans)	24	82	34	65	41	23
6	5% THF in DMTHF (v/v) (99% cis and 1% trans)	12	87	66	69	19	51
		24	98	42	66	51	25
		72	99	30	60	63	21
7	2,5% THF in DMTHF (v/v) (99% cis and 1% trans)	12	80	47	78	30	43
		24	81	33	67	45	34
		120	83	17	47	62	24
8	MTHF	12[e]	55	50	80	4	65
		24	97	77	71	14	39
9	TMTHF	12	50	31	36	5	35
		24	75	25	27	32	6
10	DEE	12	46	22	64	23	4
		24	70	17	20	53	3[f]
11	DME	12	74	42	76	31	16
		24	86	26	52	59	9

[a] The reactions were carried out using excess of **1** at 0-20 °C. Experiments 1(b), 7 and 11 were carried out at 20 °C. By-products were less than 10 % except in 1(b), 8 and 9. [b] The % conversion is the area % of all the peaks in the chromatogram including by-products. [c] % yields is the area % of the all products including by-products and % ee's as the area % of the separate peaks from the (*S*)- and (*R*)-isomers. [d] Reported yield is 78% (82-83% ee).[4] [e] After 12 hours an additional amount of *n*-BuLi equivalent to unreacted **2** was added. [f] (*R*)-isomer.



Scheme 3

The striking difference between the results obtained in THF and the other more sterically demanding solvents may have its origin in aggregation of reactants and difference in solvation of the aggregates. It has previously been suggested[3b] that the deprotonation of **2** by **1** takes place within a co-ordination complex between **1** and **2** and in the reaction a new complex between the lithium alkoxide of **3** (**3**Li) and the diamine corresponding to **1** is formed. It should be mentioned that Rickborn and co-workers[12] observed minor amounts of **4** in the ring opening of **2** with various lithium alkylamides in diethylether.

Obviously the products from the deprotonation of **2** are not capable alone of rearranging **3Li** to the homoallylic alkoxide **4Li**. An excess of **1** compared with **3Li** is necessary for opening up the pathway for isomerization of **3Li** to **4Li**. The isomerization might take place within an aggregate formed between **1** and **3Li**. Such an aggregate may be more weakly solvated in the more sterically demanding solvents. As a result the intramolecular reactivity towards the 1,3-proton transfer is dramatically increased. Clearly the rearrangement of **3Li** to **4Li** is at least partially stereospecific. The interference of e.g. the 1,3-proton transfer reaction of (*S*)-**4Li** to (*R*)-**4Li** and the reversible formation of **3Li** from **4Li** result in racemization of the two isomers. Thus the use of this reaction for stereoselection is limited by the further isomerizations if these are not inhibited.

The detailed mechanism and the preparative potential of the reported transformation of allylic alcohols into homoallylic ones are presently under investigation in our laboratories.

Acknowledgement: We thank Swedish Natural Science Research Council for financial support.

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8. Chiral columns with stationary phases octakis (6-*O* -methyl-2,3-di-*O*-pentyl)-α–cyclodextrin and heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β–cyclodextrin supplied by König (König, W. A.; Guhrcke, B.; Icheln, D.; Evers, P; Dönnecke, J.; Wang, W., *J. High Resolut. Chromatogr.* **1992**, 15, 367-372).
9. (a) To an ice-cold solution of diamine precursor of **1** (0.61 mmol) in 2 ml of 2,5-DMTHF, 0.61 mmol of *n*-BuLi (1.7 M in hexane) was added and kept at 0°C for 30 minutes. Cyclohexene oxide (0.51 mmol) was added and reaction mixture was allowed to reach ambient temperature. At intervals, 10 μl of the sample was withdrawn and the reaction was quenched with 100 μl of ammonium chloride solution, neutralized with 0.5 M HCl, washed with brine and water, dried over anhydrous sodium sulphate and injected (1 μl) on the GC column; (b) Cyclohexene oxide and (±)-2-cyclohexen-1-ol were commercially available; (c) We thank Professor König for a gift of a mixture of (±)-2-cyclohexen-1-ol and (±)-3-cyclohexen-1-ol. It was also prepared according to Crandall, J. K.; Chang, L-Ho. *J. Org. Chem.*, **1967**, 32, 435-439; (d) The diamine precursor of **1** was prepared according to literature methods.[3a-c, 3f]
10. A Fischer SPALTROHR distillation column was used to separate the 2,5-DMTHF (52% cis and 48% trans mixture) into corresponding 99% cis and 98% trans-isomers and analysed by GC.
11. Reactions were performed as mentioned in 9 (a). Instead of cyclohexene oxide, 0.21 mmol of (±)-2-cyclohexen-1-ol was added. Workup as usual. The reactions were followed by GC up to 48 hours.
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(*Received in UK* 27 *November* 1995)