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Enantioselective catalytic rearrangement of cyclohexene oxide with new homochiral bis-lithium amide bases

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Abstract—Cyclohexene oxide can be rearranged with good levels of induction (up to 68% ee) with substoichiometric amounts of chiral bases derived from readily available diamines. The influence of the steric bulk of the amine substituents on the rearrangement enantioselectivity has also been studied.

1. Introduction

The asymmetric base-mediated rearrangement of *meso*-epoxides into optically active allylic alcohols is a reaction of great interest since allylic alcohols are useful intermediates for organic synthesis. This transformation has been extensively studied during the last two decades[1] and has been applied to the synthesis of a number of commercially and biologically important substances, such as carbovir,[2] lasiol,[3] faranal,[4] leukotrienes[5] and prostaglandin precursors.[6] The best results for the asymmetric epoxide rearrangement have been obtained by Andersson et al.,[7] who have developed a chiral lithium amide, which allows the isomerisation of several epoxides with enantioselectivities up to 99% ee. They also found that the presence of an additive such as DBU was essential to achieve optimum enantioselectivities. Our group has also investigated the enantioselective deprotonation of *meso*-epoxides with bis-lithium amides derived from C_2 symmetric diamines.[8] The best result for the enantioselective deprotonation of cyclohexene oxide **1** was been obtained with the bis-lithium amide base (*R*,*R*)-**2**. This chiral base gave the allylic alcohol (*R*)-**3** in good yield (68%), with an enantiomeric excess of 76% (Table 1, entry 1). Use of LDA to regenerate the original bis-lithium amide (*R*,*R*)-**2** gave the allylic alcohol (*R*)-**3** with a significantly lower enantiomeric excess (entry 2). The addition of DBU has not allowed to enhance the enantioselectivity of the rearrangement (entry 3). Surprisingly, efficient recycling was observed when a strong carbon base such as *n*-BuLi or MeLi was used (entries 4–6).

Herein we report preliminary results obtained in the catalytic enantioselective deprotonation of cyclohexene oxide **1** using new homochiral bis-lithium amide bases. The reactions have been carried out in THF rather than in benzene because we observed a huge decrease of the reactivity of the chiral amide in this solvent. We have obtained similar results than with bis-amide (*R*,*R*)-**2**. The main advantage of these new chiral bases is that they can be prepared easily in only one or two steps. We have varied the steric bulk of their substituents α to the nitrogen in order to study their influence on enantioselectivity.

2. Results and discussion

The diamines **4**–**8** were prepared in two steps: first formation of the diimine by condensation of 2 equiv of the corresponding amine with an aq solution of glyoxal,[10] and then reduction of the diimine with $NaBH_4$ in MeOH (Scheme 1).

We obtained 45% enantiomeric excess (ee) for the asymmetric rearrangement of cyclohexene oxide **1** to 2-cyclohexen-1-ol **3** using MeLi (1 equiv) in the presence of substoichiometric amounts (0.2 mol%) of base Li-**4** (Table 2, entry 1). Replacement of the methyl groups in Li-**4** by ethyl groups increased the ee from 45% to 59% (entry 2). We thought that replacement of the phenyl groups in Li-**4** by 1-methoxyphenyl groups could enhance the stereocontrol of the deprotonation.

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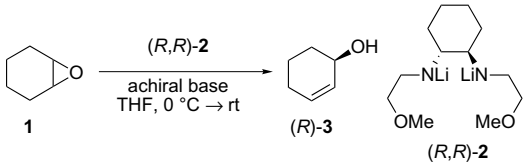
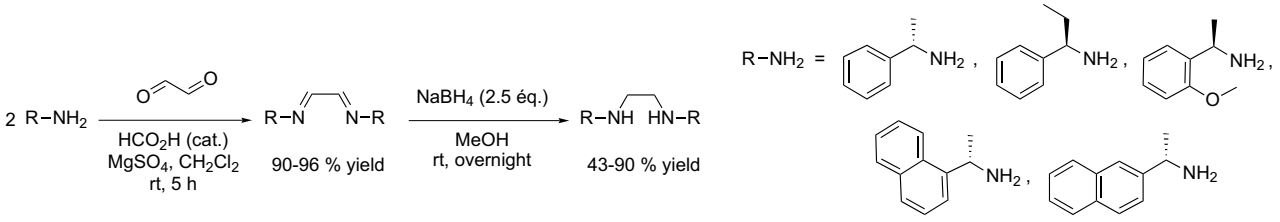
Table 1. Enantioselective rearrangement of cyclohexene oxide **1** with chiral base (*R*,*R*)-**2**



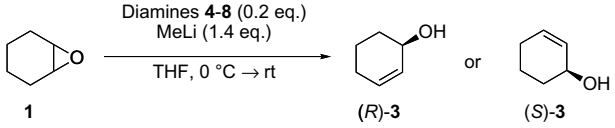
Entry	(*R*,*R*)-**2**	Achiral base	Additive	Time (h)	Yield (%)[a]	Ee (%)[b]
1	1.0 equiv	—	—	21	68	76 (*R*)
2	0.2 equiv	LDA (1.0 equiv)	—	22	66	32 (*R*)
3	0.2 equiv	LDA (1.0 equiv)	DBU (6 equiv)	43	35	13 (*R*)
4	0.2 equiv	MeLi (1.0 equiv)	—	20	54	60 (*R*)
5	0.2 equiv	MeLi (1.0 equiv)[c]	—	68	56	67 (*R*)
6	0.2 equiv	*n*-BuLi (1.0 equiv)[c]	—	48	47	67 (*R*)

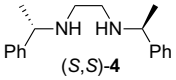
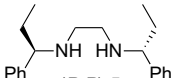
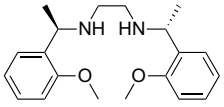
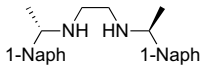
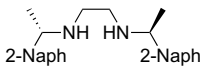
[a] Isolated yield after flash chromatography.
[b] Enantiomeric excess determined by ^{31}P NMR analysis.[9]
[c] Reaction carried out in benzene.



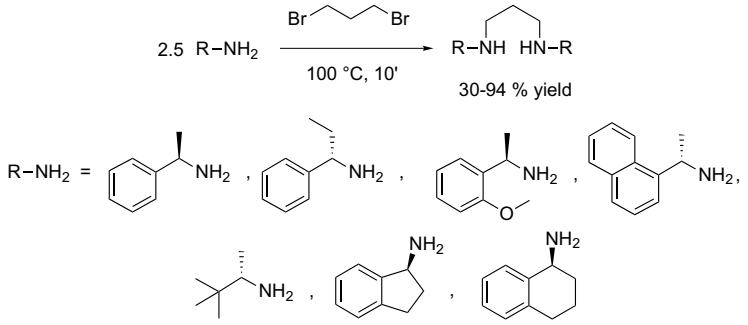
Scheme 1. Formation of 1,2-ethane-diamines **4**–**8**.

Table 2. Enantioselective rearrangement of cyclohexene oxide **1** with chiral bases Li-**4**–**8**



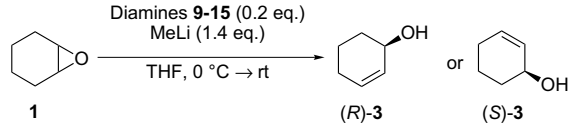
Entry	Chiral base	Time (h)	Yield (%)[a]	Ee (%)[b]
1	 (*S*,*S*)-**4**	21	80	45 (*S*)
2	 (*R*,*R*)-**5**	23	80	59 (*R*)
3	 (*R*,*R*)-**6**	4 days	71	56 (*S*)
4	 (*S*,*S*)-**7**	39	63	40 (*S*)
5	 (*S*,*S*)-**8**	46	57	34 (*S*)

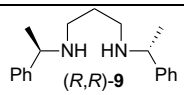
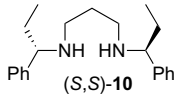
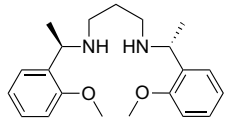
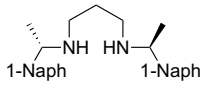
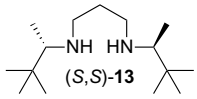
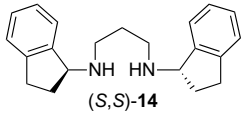
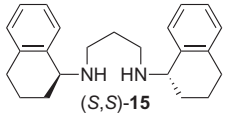
[a] Isolated yield after flash chromatography.
[b] Enantiomeric excess determined by chiral-GC on HYDRODEX B-3P.



Scheme 2. Formation of 1,3-propane-diamines **9**–**15**.

Table 3. Enantioselective rearrangement of cyclohexene oxide **5** with chiral bases Li-**9**–**15**



Entry	Chiral base	Time (h)	Yield (%)[a]	Ee (%)[b]
1	 (*R*,*R*)-**9**	72	62	57 (*R*)
2	 (*S*,*S*)-**10**	63	60	57 (*S*)
3	 (*R*,*R*)-**11**	4 days	29[c]	10 (*S*)
4	 (*S*,*S*)-**12**	45	49	68 (*S*)
5	 (*S*,*S*)-**13**	6 days	36[d]	8 (*S*)
6	 (*S*,*S*)-**14**	40	67	16 (*R*)
7	 (*S*,*S*)-**15**	42	63	39 (*S*)

[a] Isolated yield after flash chromatography.
[b] Enantiomeric excess determined by chiral-GC on HYDRODEX B-3P.
[c] Conversion: 55%.
[d] Formation of *trans*-2-methyl-cyclohexan-1-ol (11%).

Additional ligation in the bis-lithium amide should increase the rigidity of the base. Unfortunately, the presence of the methoxy groups did not improve the ee obtained with Li-**5** (entry 3). Replacement of the phenyl groups in Li-**1** by either 1-naphthyl or 2-naphthyl groups was unsuccessful (entries 4 and 5). The ee's were slightly lower than those obtained with base Li-**4** (40% and 34%, respectively). In the case of the bases

derived from 1,2-diamino-ethane, replacement of the methyl groups by ethyl groups was favourable in terms of enantioselectivity for the asymmetric rearrangement of cyclohexene oxide **1**.

In order to see if such an improvement could also be achieved with bases derived from 1,3-propane-diamine, we have prepared the diamines **9**–**15**. They have been prepared in one step, by nucleophilic substitution of 1,3-dibromo-propane with 2.5 equiv of the corresponding amine (Scheme 2).[11]

The base Li-**9** was first evaluated. We obtained 57% ee for the enantioselective deprotonation of cyclohexene oxide **1** (Table 3, entry 1). In this case, replacement of the methyl groups in Li-**9** by ethyl groups had no effect on the enantioselectivity of the rearrangement. We obtained exactly the same ee (entry 2). Replacement of the phenyl groups in Li-**9** by 1-methoxy groups had a very detrimental effect on enantioselectivity, as the ee dropped to 10% (entry 3). Replacement of the phenyl groups in Li-**9** by 1-naphthyl groups increased the enantiomeric excess from 57% to 68% (entry 4), which is the best ee obtained to date with a homochiral bis-lithium amide for the enantioselective deprotonation of cyclohexene oxide **1**.[8] We have also tried to replace the phenyl groups in Li-**9** by *tert*-butyl groups. The base Li-**13** afforded 2-cyclohexen-1-ol **3** with only 8% ee and 36% yield (entry 5). The replacement of the phenyl groups by alkyl groups had a detrimental effect on enantioselectivity and on reactivity. Indeed, we observed the formation of product of opening by MeLi (11%). Finally, we have tested the bases Li-**14** and Li-**15**, which possessed a cyclic substituent in α of the nitrogen atoms. We thought that such a unit would bring less flexibility to our system, thus inducing better enantioselectivity. However, in both cases, the ee's were lower. The ee's dropped from 45% to 16% and 39%, respectively (entries 6 and 7). Thus, in the case of the bases derived from 1,3-diamino-propane, replacement of the methyl groups by 1-naphthyl groups was favourable in term of enantioselectivity for the asymmetric rearrangement of cyclohexene oxide **1**.

3. Conclusion

In conclusion, we have shown that fine tuning of the substituents of the amine moiety improved the enantioselectivity for the base-mediated epoxide rearrangement of cyclohexene oxide. We were able to rearrange cyclohexene oxide **1** with ee up to 68% with really easily available diamines. Further developments are under studies in order to increase the catalyst efficiency and results will be reported in due course.

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References and notes

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