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# Catalytic enantioselective deprotonation of *meso*-epoxides utilising homochiral bis-lithium amide bases

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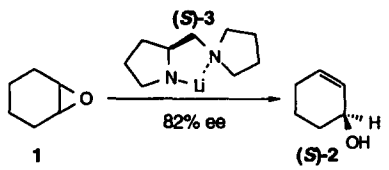
***Abstract:*** (*R*)-2-Cyclohexen-1-ol and (*R*)-2-cyclooctene-1-ol have been prepared in very good ee using *R,R*-homochiral bis-lithium amide bases derived from homochiral $C_2$ symmetric diamines. (*R*)-2-Cyclohexen-1-ol has been synthesized in good ee utilising catalytic homochiral bis-lithium amide in the presence of *n*-butyl lithium. © 1997 Elsevier Science Ltd

Homochiral lithium amides have been exploited by a variety of efficient asymmetric methods for the synthesis of non-racemic chiral compounds.[1] The rearrangement of epoxides to allylic alcohols induced by lithium amides is well known.[2] The first non-enzymatic asymmetric version of this rearrangement was published by Whitesell and Felman who treated cyclohexene oxide **1** with a variety of homochiral mono- and di-alkyl lithium amides.[3] However, the resulting (*R*)-2-cyclohexen-1-ol (***R*)-2** was obtained in no greater than 36% ee.

More recently, much research has been directed towards improving the level of asymmetric induction of this rearrangement using a variety of homochiral lithium amides.[4] Asami has used a series of homochiral lithium amides derived from (*S*)-proline, which have achieved a maximum 79% ee for the conversion of cyclohexene oxide **1** to (*S*)-2-cyclohexen-1-ol (*S*)-**2** (Scheme 1).[4a,b,g]




**Scheme 1.**

This enantioselective deprotonation reaction has been applied to the synthesis of a number of key cyclopentenoid intermediates, which can be elaborated to important biologically-active compounds such as prostaglandins.[5] Thus, continuing research in this area and efforts to generate catalytic homochiral base systems to effect enantioselective deprotonation of *meso*-epoxides are of current interest.

Murphy[5f] and Hodgson[4k] have taken the dilithium salts of (1*R*,2*S*)- and (1*S*,2*R*)-norephedrine, to effect enantioselective deprotonation of functionalised cyclopentene oxides with excellent enantiomeric excesses of the resulting allylic alcohols. We wish to report that high levels of asymmetric induction can be achieved for the enantioselective deprotonation of cyclohexene oxide **1** and cyclooctene oxide **6**, utilising homochiral bis-lithium amides[6] **5a–d** derived from $C_2$ symmetric homochiral diamines **4a–d** (Scheme 2). These diamines **4a–d** were readily prepared by methods developed in our laboratory.[7]

The diamines used varied in the chelating properties and steric bulk of their substituents $R_1$ and $R_2$. We have studied the enantioselective deprotonation of cyclohexene oxide **1** using homochiral bis-lithium amides **5a–d** (Table 1). The absolute configuration of the major enantiomer of the product

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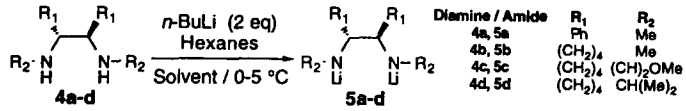
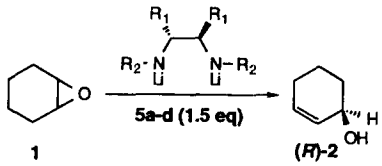



Scheme 2.

Table 1.




| Amide | Conditions | Yield | ee |
|---|---|---|---|
| **5a** | THF, 0°C then at rt, 21 h | 27% | 46% (*R*) |
| **5c** | THF, 0°C then at rt, 21 h | 68% | 76% (*R*) |
| **5c** | PhH, 5°C then at rt, 71 h | 42% | 75% (*R*) |
| **5c** | THF, LiCl (1.5 eq), 0°C then at rt, 46 h | 55% | 55% (*R*) |
| **5c** | PhH, LiCl (1.5 eq), 0°C then at rt, 46 h | 35% | 50% (*R*) |

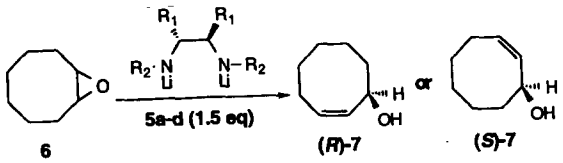
allylic alcohols was obtained from the sign of specific rotation.[8] The ee's of the allylic alcohols resulting from enantioselective deprotonation of the *meso*-epoxides were determined by $^{31}P$ NMR analysis of the diastereomeric diazaphospholidines or thiophosphonamides prepared, using our established method of determining the ee's of alcohols.[9]

Singh has reported the best to date ee for the rearrangement of cyclohexene oxide **1** to (*S*)-2-cyclohexen-1-ol (***S*)-2** of 80% ee, using an (*R*)-phenylglycine/piperidine-derived amide base ((*R*)-2-cyclohexen-1-ol (***R*)-2** was obtained in 72% ee).[4e,f] Our best ee for the conversion of cyclohexene oxide **1** to (*R*)-2-cyclohexen-1-ol (***R*)-2** was 76% ee, when enantioselective deprotonation was carried out with the homochiral bis-lithium amide base **5c** in THF. No enhancement in ee was observed when deprotonation was performed in the presence of lithium chloride (1.5 eq) in THF. Simpkins had found that the addition of lithium chloride enhanced enantioselectivity in the enolisation of symmetrical cyclic ketones using homochiral lithium amide bases.[10] In addition, we have been able to recover the regenerated homochiral $C_2$ symmetric diamines **4a–d** in high yield (75–85%) with no loss of ee, by acid–base extraction followed by short-path distillation of the crude diamine. This factor of recyclability of the homochiral diamines **4a–d** further vindicates our methodology.

Furthermore, we have studied the enantioselective deprotonation of cyclooctene oxide **6** (Table 2). Previously in the literature, Asami had reported the highest ee of 58% for the conversion of cyclooctene oxide **6** to (*S*)-2-cyclooctene-1-ol (***S*)-7** using homochiral lithium amide base (***S*)-3** derived from (*S*)-proline.[4a]

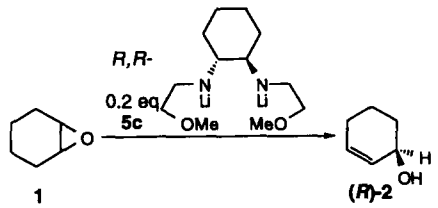
We have achieved the highest recorded ee for the conversion of cyclooctene oxide **6** to (*R*)-2-cyclooctene-1-ol (***R*)-7**, using homochiral bis-lithium amide base **5c** in benzene. Homochiral bis-lithium amide base **5c** gave superior enantiomeric excesses of the allylic alcohol (***R*)-7** compared to the amide bases **5a,b,d**, irrespective of the solvent or conditions used. We believe that the methoxy moieties of the $R_2$ substituents of the amide base **5c** may be acting as additional ligation sites for chelation between the aggregate of the base **5c** and the epoxide **6**. The best ee of (*R*)-2-cyclooctene-1-ol (***R*)-7** was obtained in benzene which is a non-coordinating solvent unlike THF. Using HMPA as an additive in THF had a detrimental effect on the reactivity and enantioselectivity of the amide base **5c**, which may be a consequence of the donor solvent interfering in the chelation between the base **5c** and the epoxide **6**. This observation is in contradiction to Asami's results, which have shown that

Table 2.




| Amide | Conditions | Yield | ee |
|---|---|---|---|
| **5a** | THF, -80°C then at rt, 49 h | 23% | 4% (*R*) |
| **5b** | THF, -80°C then at rt, 72 h | 59% | 21% (*S*) |
| **5d** | THF, -80°C then at rt, 19 h | 77% | 32% (*R*) |
| **5c** | THF, -80°C then at rt, 48 h | 30% | 77% (*R*) |
| **5c** | THF, *n*-BuLi (1.5 eq), -80°C then at rt, 48 h | 56% | 76% (*R*) |
| **5c** | PhH, 5°C then at rt, 44 h | 49% | 87% (*R*) |
| **5c** | THF, HMPA (6 eq), -80°C then at rt, 72 h | 38% | 55% (*R*) |

Table 3.




| Conditions | Yield | ee |
|---|---|---|
| *n*-BuLi (1 eq) Hexanes / PhH, 5°C then at rt, 48 h | 47% | 67% (*R*) |
| LDA (1.5 eq) Hexanes / THF, 0°C then at rt, 22 h | 66% | 32% (*R*) |
| LDA (1.5 eq), DBU (6 eq), Hexanes / THF, 0°C then at rt, 43.5 h | 35% | 13% (*R*) |

HMPA enhances the reactivity and enantioselectivity of the homochiral lithium amide bases derived from (*S*)-proline in the deprotonation of *meso*-epoxides.[4a] Also, it appears that the yield of the allylic alcohol (***R*)-7** can be improved with virtually no change in ee, when additional *n*-BuLi (1.5 eq with respect to **6**) is used in THF. The results seem to suggest the role of aggregrates of the base **5c** in the enantioselective deprotonation of cyclohexene oxide **1** and cyclooctene oxide **6**.

Asami has reported the sole example of catalytic enantioselective deprotonation of *meso*-epoxides including cyclohexene oxide **1**, using 0.2 eq of the homochiral lithium amide base (***S*)-3** in combination with 1 eq lithium diisopropylamide (LDA) and 6 eq 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in THF.[11] The resulting (*S*)-2-cyclohexen-1-ol (***S*)-2** was obtained in 71% yield and 75% ee. We wish to reveal our preliminary results of the catalytic enantioselective deprotonation of cyclohexene oxide **1** employing homochiral bis-lithium amide base **5c** (Table 3).

These encouraging early results have indicated that *n*-BuLi in benzene is able to regenerate the catalyst of the homochiral bis-lithium amide base **5c** *in situ* and provide (*R*)-2-cyclohexene-1-ol (***R*)-2** in much better enantiomeric excess than LDA in THF. Studies are continuing to optimise the catalytic enantioselectivity of the homochiral bis-lithium amide base **5c** in the deprotonation of cyclohexene oxide **1** and other *meso*-epoxides.

In summary, we have discovered that homochiral bis-lithium amide bases **5a–d** are capable of promoting asymmetric induction in the deprotonation of *meso*-epoxides **1** and **6**. These homochiral

bis-lithium amide bases **5a–d** are accessible from readily synthesized homochiral $C_2$ symmetric diamines **4a–d**.[7] Homochiral bis-lithium amide base **5c** was found to be the most enantioselective base giving (*R*)-2-cyclohexene-1-ol (***R*)-2** and (*R*)-2-cyclooctene-1-ol (***R*)-7** in very good ee's from their respective *meso*-epoxides **1** and **6**, when used in more than stoichiometric quantities. We have been able to recover the respective homochiral $C_2$ symmetric diamines **4a–d** from these reactions in high yield with no loss in ee. Preliminary results indicate that catalytic enantioselective deprotonation of *meso*-epoxides is viable using a catalytic quantity of the homochiral bis-lithium amide base **5c**, in combination with a stoichiometric quantity of an organolithium or lithium amide. We will report the results of our continuing studies shortly.

**Acknowledgements**

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