Communications to the Editor

New and Highly Enantioselective Catalysts for the Rearrangement of *meso*-Epoxides into Chiral Allylic Alcohols

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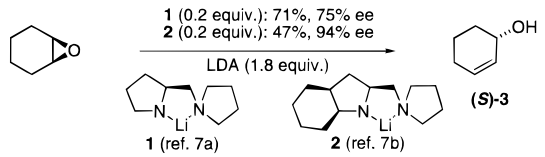
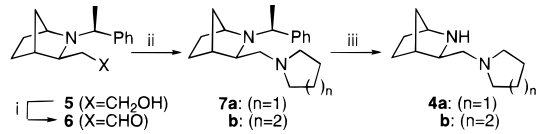
The asymmetric base-mediated rearrangement of *meso*-epoxides into optically active allylic alcohols is a reaction of great interest since allylic alcohols are useful intermediates for organic synthesis.[1] As a consequence, this transformation has been employed as the key step in the syntheses of numerous commercially and biologically important substances, for example, carbovir,[2] lasiol,[3] faranal,[4] leukotrienes,[5] and prostaglandin precursors.[6] The reaction is, however, sowewhat limited since it generally requires 1.5−2 equiv of a chiral base. Although it has been found that adequate enantioselectivity could be retained using **1** or **2** in less than stoichiometric amounts, (Scheme 1),[7] a versatile catalyst, highly enantioselective for a variety of substrates and readily accessible in both enantiomeric forms, remains to be found.

We herein report our initial studies of the preparation of the 3-aminomethyl-2-azabicyclo[2.2.1]heptanes **4a**−**b** (Scheme 2),[8] and the use of their Li-amides as catalysts for the title reaction. We reasoned that a Li-amide having a more rigid backbone than **2** would adopt a more well-ordered TS in the deprotonation reaction and give rise to higher asymmetric induction as the result of a more strict discrimination between the enantiotopic protons in the substrate. For this purpose, we have developed a straightforward and high-yielding route to diamines **4** in either enantiomeric form (Scheme 2). Enantiopure amino alcohol **5**[8d] is simply oxidized to aldehyde **6**, which gives the catalyst precursors **4** after a one-pot reductive amination and subsequent N-debenzylation. Considering its high overall yields and enantiodivergence, this approach should offer a practical and flexible alternative to the existing methods for preparing this kind of diamine derivatives.[9]

Scheme 1

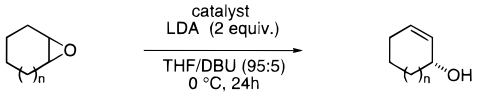


Scheme 2[a]



[a] **Reagents and conditions**: (i) Swern ox. (98%). (ii) a: pyrrolidine; b: piperidine; MS 3A, methanol, then $NaBH_3CN$ (a: 83; b: 91%). (iii) H_2 (1 atm), $Pd(OH)_2/C$; methanol/AcOH (a: 89; b: 93%).

Table 1.



entry	epoxide	catalyst	mol %	% yield[a]	ee[b]	absolute config[c]	product
1	$n = 0$	**4a**	120	78[d]	95	*R*[e]	**8**
2	$n = 0$	**4a**	15	67[d]	49	*R*	**8**
3	$n = 1$	**4a**	120	87	97	*R*[e]	**3**
4	$n = 1$	**4a**	5	91	96	*R*	**3**
5	$n = 1$	*ent*-**4a**[f]	5	90	95	*S*	**3**
6	$n = 1$	**4b**	5	85	93	*R*	**3**
7	$n = 2$	**4a**	120	93	98	*R*[g]	**9**
8	$n = 2$	**4a**	5	89	96	*R*	**9**
9	$n = 3$	**4a**	120	84	81	*R*[e]	**10**
10	$n = 3$	**4a**	5	81	78	*R*	**10**
11	(*Z*)-4-octene-oxide	**4a**	120	88	67[h]	*R*[e]	**11**
12	(*Z*)-4-octene-oxide	**4a**	5	82	66[h]	*R*	**11**

[a] Isolated. Conversions >90% (determined by GLC using *n*-dodecane as internal standard. [b] Determined by GLC (Chrompack Chirasil Dex-CB). [c] Assignment based on the sign of optical rotation. [d] After benzoylation (ref 7b). Reaction was run at rt. [e] See ref 6b. [f] Enantiomer of **7a**. [g] See ref 14. [h] Determined by analysis of the (*R*)-MTPA ester (^{1}H NMR, 400 MHz).

The catalytic ability of these new bases was evaluated using the conditions developed by Asami,[7] that is, the reactions were carried out by adding a solution of the *meso*-epoxide to a catalyst mixture containing LDA as the stoichiometric base and DBU as cosolvent in THF.[10] Our preliminary results are presented in Table 1. The levels of asymmetric induction for the cyclic epoxides are, to our knowledge, the highest reported so far for

(1) Reviews: (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (b) Asami, M. *J. Synth. Org. Chem., Jpn.* **1996**, *54*, 188. (c) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. (d) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. (e) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345.

(2) (a) Hodgson, D. M.; Whiterington, J.; Moloney, B. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3373. (b) Hodgson, D. M.; Gibbs, A. R. *Synlett* **1997**, 657. (c) Asami, M.; Takahashi, J.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1649. (d) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 167.

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(4) Mori, K.; Murata, N. *Liebigs Ann. Chem.* **1995**, 2089.

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(7) (a) Asami, M.; Ishizaki, T.; Inoue. S. *Tetrahedron: Asymmetry* **1994**, *5*, 793. (b) Asami, M.; Suga, T.; Honda, K.; Inoue. S. *Tetrahedron Lett.* **1997**, *38*, 6425. (c) Tierney, J. P.; Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1019.

(8) Optically pure *exo*-2-azabicyclo[2.2.1]heptane-3-carboxylic acid derivatives have previously been used for the preparation of chiral catalysts: (a) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530. (b) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. J. *Org. Chem.* **1998**, *63*, 2749. (c) Södergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577. (d) Both enantiomers of amino alcohol **5** are available in three steps from cheap starting materials and on a multigram scale; Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1700. (e) Stella, L.; Abraham, H.; Feneau-Dupont, J,: Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603. (f) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045. (g) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

(9) The amide-coupling step in the preparation of diamine derivatives related to **1** (as described in ref 6b) has been reported to be troublesome, and alternative strategies have been described: (i) Optimization of reagents and conditions to minimize racemization in the coupling of phenylglycine derivatives, see ref 6d. (ii) Construction of the tertiary amine moiety via nucleophilic substitution: (a) Hendrie, S. K.; Leonard, J. *Tetrahedron* **1987**, *14*, 3289. (b) Alker, D.; Doyle, K. J.; Harwood: L. M.; McGregor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 877. (c) de Sousa, S. E.; O'Brien, P.; Poumellec, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2613. (d) See ref 2d.

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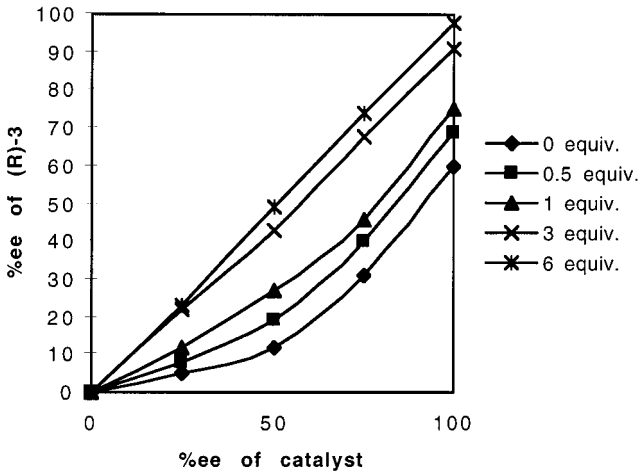

Figure 1. Asymmetric induction versus enantiomeric purity of catalyst **4a**. Influence of DBU as cosolvent.

the asymmetric epoxide deprotonation (entries 1−10, Table 1). It is also the first example of a catalytic system for this reaction which, except for cyclopentene oxide (entries 1−2, Table 1),[11] gives very high enantioselectivity regardless of whether a full equivalent or 5 mol % of the chiral base is used (cf. entries 3−4, 7−8, 9−10, and 11−12, respectively, Table 1).

The presence of a chelating cosolvent like HMPA or DBU has often been observed to have a beneficial influence on the enantioselectivity in base-mediated epoxide rearrangements. It has been suggested that such additives inhibit the formation of reactive but unselective aggregates of the chiral Li-amides.[1c,2c,6a−b] To test this hypothesis, a series of experiments was carried out where cyclohexene oxide was reacted in the presence of a catalyst generated from partly racemic diamine **4a** and varying amounts of DBU. The results are shown in Figure 1 where the ee of the obtained (*R*)-2-cyclohexenol **3** is plotted versus the enantiomeric purity of **4a**. At high DBU concentrations, the relationship between the ee's of the catalyst and the product is strictly linear, whereas a pronounced negative nonlinear relationship is observed at intermediate catalyst enantiopurity with lower DBU loadings. The fact that the presence of DBU increases the enantioselectivity of the enantiopure catalyst supports the idea that DBU inhibits the formation of kinetically competent but less enantioselective aggregates of type $(Li^+\mathbf{4a}^-)_n$. The linear relationship between the catalyst and the product ee indicates that the active catalyst is mainly monomeric (or a $Li^+\mathbf{4a}^-$•DBU heterodimer) in the presence of DBU of sufficient concentration. The nonlinear effect could be explained by the action of heterochiral, *meso*-type aggregates $(Li^+\mathbf{4a}^-•Li^+\textit{ent}\text{-}\mathbf{4a}^-)_n$, for which DBU-assisted dissociation occurs more easily than for the corresponding homochiral dimers.[12] This would thus give a monomeric catalyst of lower enantiomeric purity than that of the original **4a**. Another explanation which would account for the observed nonlinear effect would be the formation of *meso*-type aggregates having a superior catalytic activity for the formation of racemic product.

In conclusion, we have developed an efficient route to both enantiomers of diamines **4** and, in a preliminary study, have found their Li-amides to be highly efficient catalysts for the asymmetric base-mediated rearrangement of epoxides. Cyclic *meso*-epoxides gave the corresponding chiral 2-cycloalken-1-ol derivatives of excellent ee, even at very low catalyst loading. Furthermore, a study of the relationship between asymmetric induction in the reaction and enantiomeric purity of the catalyst efficiently illustrates how DBU can improve the catalytic performance by preventing the formation of less selective Li-amide aggregates. Extended studies of diamine catalysts of this family are underway, including the development of catalysts with altered steric properties,[13] additional chelation sites and/or stereocentra as well as their application in total synthesis, and ab initio calculations, aiming to find a rationale for the origin of the asymmetric induction.

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Supporting Information Available: Experimental procedures, methods for determination of enantiomeric mixtures, characterization data for new compounds (6 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(10) The reaction of cycloheptene oxide (entry 8, Table 1) was carried out using a representative procedure. To a solution of **4a** (50 μmol), DIPA (2.0 mmol) and DBU (5.0 mmol; 0.75 mL) in dry THF (4 mL) under Ar at 0 °C was added *n*-BuLi (2.0 mmol, 1.6 M in hexanes) dropwise during 5 min. The resulting yellowish solution was stirred at 0 °C for another 30 min, and cycloheptene oxide (1 mmol) in THF (3.5 mL) was then added dropwise during 5 min. The reaction mixture was kept for 24 h at 0 °C before it was partitioned between saturated aqueous NH_4Cl (5 mL) and Et_2O (15 mL). The phases were separated and the ether layer washed with 2 M HCl (2 × 5 mL), water (5 mL), brine (5 mL), and dried ($MgSO_4$). Enantiomeric excess was determined using a sample from this mixture to be 96% ee by using GLC with a chiral stationary phase (Chirasil Dex-CB). The crude alcohol was coated on silica gel by evaporation of the solvent and directly purified by column chromatography to give (*R*)−**9** (89%) as a colorless oil.

(11) Cyclopentene oxide needs higher reaction temperatures than higher homologues (see ref 6b), and there is no report describing its catalytic rearrangement. The highest reported enantioselectivity (41% ee) was obtained using 1.5 equiv of Li-amide **1** (Scheme 1).

(12) About nonlinear effects in asymmetric catalysis, see, e.g.: (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.

(13) Diamine derivatives bearing substituents in α-position to the tertiary amine would be of particular interest since such catalysts could be expected to give severe steric repulsions with the substrate in the TS of the disfavored pathway of the reaction. For related mechanistic studies, see: Kahn, A. Z.-Q.; deGroot, R. W.; Arvidsson, P. I.; Davidsson, Ö. *Tetrahedron: Asymmetry* **1998**, *9*, 1223.

(14) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.