Enantioselective α-deprotonation–rearrangement of *meso*-epoxides

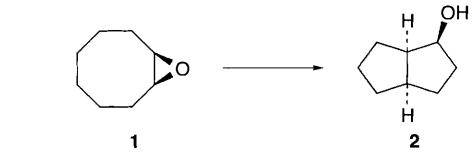
David M. Hodgson* and Gary P. Lee

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY† and Department of Chemistry, The University of Reading, Whiteknights, Reading, UK RG6 2AD

Enantioselective α-deprotonation–rearrangement of medium-sized (8-, 9- and 10-membered) cycloalkene-derived *meso*-epoxides using organolithiums in the presence of (−)-sparteine gives bicyclic alcohols in good yields and ees.

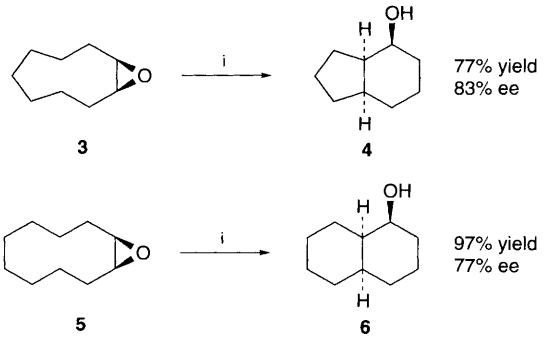
Enantioselective desymmetrisation of *meso*-materials is an attractive and potentially extremely powerful concept in asymmetric synthesis. A number of strategies are already known which demonstrate the viability of this concept and its application in targeted syntheses to provide compounds with high ee.[1] *meso*-Epoxides represent an important class of substrates which can be used to develop new desymmetrisation methodology because they are easily prepared with predictable stereochemistry directly from alkenes. The enantioselective rearrangement of *meso*-epoxides to allylic alcohols using non-racemic bases has been the focus of much research.[2] However, enantioselective rearrangements which proceed *via* metallation of the epoxide ring have not, to our knowledge, been examined. One class of epoxides, derived from medium-sized cycloalkenes, are known to undergo this metallation to give racemic bicyclic alcohols (*e.g.* Scheme 1).[3] Here we report our preliminary results concerning the development of an asymmetric variant of this transformation.

In 1977 Boeckman reported that the epoxides **1** and **5** (Scheme 2) rearranged cleanly to the bicyclic alcohols **2** and **6** respectively, on treatment with BuLi (3 equiv.) in diethyl ether–hexane at −78 °C for 3 h followed by warming to room temperature.[4] This led us to consider the combination of an organolithium with a nonracemic ligand as a method for enantioselective epoxide desymmetrisation. As Hoppe *et al.* had found that highly enantioselective deprotonation α to oxygen in carbamates was possible when using Bu^{s}Li in combination with



1 **2**

Scheme 1



3 **4**

5 **6**

Scheme 2 *Reagents and conditions*: i, Pr^{i}Li (2.4 equiv.), (−)-sparteine (2.5 equiv.), Et_2O, −98 °C (5 h) to 25 °C (15 h)

(−)-sparteine in diethyl ether,[5] we initially applied these conditions[5a] to the epoxide **1**, to give the alcohol **2** in good yield and ee (Table 1, entry 1).‡

Importantly, the combination of the diamine with the organolithium did not compromise yield or clean conversion of the epoxide **1** exclusively to the *endo cis*-fused bicyclic alcohol **2**. No cyclooct-2-en-1-ol was observed. A secondary organolithium was essential to obtain a good level of ee in this transformation; use of BuLi or Bu^{t}Li proceeded to give the alcohol **2** in similar yields to Bu^{s}Li, but with low and no ee respectively (Table 1, entries 2 and 3). The latter observation with Bu^{t}Li parallels observations made by Beak *et al.* in the enantioselective deprotonation of *N*-Boc pyrrolidine and lends support to the argument that tertiary organolithium is not able to form a complex with (−)-sparteine that can effect enantiotopic proton selection.[6] Pr^{i}Li,[7] which unlike Bu^{s}Li does not contain a stereogenic centre,[8] gave an improved ee (entry 4). Use of the secondary organolithiums in hydrocarbon solvents (pentane or toluene) gave similar levels of ee to those found using diethyl ether, however yields of the alcohol **2** were reduced in these cases.

Quenching the reaction of the epoxide **1** with Bu^{s}Li and (−)-sparteine in diethyl ether after 5 h at −78 °C gave a similar yield and ee of alcohol **2** to that obtained from an otherwise identical reaction, but which had been allowed to warm to room temperature after 5 h at −78 °C (entry 1). These results imply that the deprotonation is operative at −78 °C. Lowering the reaction temperature to −98 °C resulted in improved ees (entries 5 and 6). It was found possible to reduce the quantity of (−)-sparteine and still achieve levels of asymmetric induction (entries 7 and 8). Although ees were reduced in these cases, these results are significant in that they indicate the potential for asymmetric catalysis. Wihin the scope of our study, the best conditions for product formation in terms of yield and ee were found to be using Pr^{i}Li (2.4 equiv.) and (−)-sparteine (2.5 equiv.) at −98 °C (entry 9).§ These conditions were also effective for the enantioselective desymmetrisation of cyclononene epoxide **3**[9] and cyclodecene epoxide **5**, to give the alcohols **4** {$[\alpha]_D^{21}$ −27.2 (*c* 1.0, $CHCl_3$)} and **6** {$[\alpha]_D^{21}$ −17.2 (*c* 1.0, $CHCl_3$)} respectively (Scheme 2).‡

Table 1 Effect of experimental conditions on the yields and enantioselectivities of formation of alcohol **2** from epoxide **1** using RLi/(−)-sparteine in diethyl ether

Entry	RLi	Sparteine : RLi : epoxide **1**	*T*/°C	Yield (%)	Ee (%)
1	Bu^{s}Li	1.45 : 1.4 : 1	−78	81	70
2	BuLi	1.45 : 1.4 : 1	−78	74	31
3	Bu^{t}Li	1.45 : 1.4 : 1	−78	74	0
4	Pr^{i}Li	1.45 : 1.4 : 1	−78	75	78
5	Bu^{s}Li	1.45 : 1.4 : 1	−98	79	73
6	Pr^{i}Li	1.45 : 1.4 : 1	−98	74	83
7	Bu^{s}Li	0.5 : 1.4 : 1	−98	58 (73)[a]	69
8	Bu^{s}Li	0.2 : 1.4 : 1	−98	53 (76)[a]	55
9	Pr^{i}Li	2.5 : 2.4 : 1	−98	86	84

[a] Yield in parentheses based on recovered epoxide **1**.

In summary, these first examples of enantioselective α-deprotonations of *meso*-epoxides demonstrate the potential of this new strategy for asymmetric synthesis. Further studies on the scope of this process (other substrates and ligands) are in progress and will be reported in due course.

We thank the EPSRC, the DTI and a consortium of chemical companies for a studentship award (to G. P. L.) through the LINK Asymmetric Synthesis 2nd CORE Programme. We also thank Merck Sharp & Dohme for carrying out preliminary HPLC analyses, The Royal Society for a Research Grant towards an HPLC system, the EPSRC Mass Spectrometry Service Centre for mass spectra and Zeneca (Strategic Research Fund) for a generous unrestricted grant.

Footnotes

† Address for correspondence.

‡ Ees were determined on the 2,4-dinitrobenzoate derivatives by HPLC [Daicel Chiralpak AD column (4.6 mm × 250 mm), 50 : 50 EtOH–hexane as eluent]. The absolute configurations of the predominant enantiomers produced with epoxides **1** and **5** are as shown in Schemes 1 and 2 and were established by comparison of the direction of the optical rotations with those of the known alcohols **2**[10] and **6**.[11] For alcohol **4**,[12] the predominant enantiomer was assigned by analogy with alcohols **2** and **6**.

§ Freshly distilled (−)-sparteine (1.13 cm^3, 4.9 mmol) was added dropwise over 0.5 h to a stirred solution of Pr^iLi[7] [1.2 mol dm^{-3} in light petroleum (bp 40–60 °C); 4.0 cm^3, 4.8 mmol] in diethyl ether (8 cm^3) at −98 °C. The reaction mixture was allowed to stir for 1 h at −98 °C before the cyclooctene epoxide **1** (252 mg, 2.0 mmol) in diethyl ether (2 cm^3) was added dropwise over 0.5 h. The reaction mixture was stirred for 5 h at this temperature and then warmed slowly to ambient temperature overnight. The reaction mixture was then cooled to 0 °C before HCl (2 mol dm^{-3} in water, 10 cm^3) was added dropwise. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2 × 10 cm^3), brine (10 cm^3), dried ($MgSO_4$) and then evaporated under reduced pressure. Purification of the residue by column chromatography [(SiO_2, 30% diethyl ether–light petroleum (bp 40–60 °C)] gave the alcohol **2** (217 mg, 86%); $[\alpha]_D^{21}$ −19.0 (*c* 1.0, $CHCl_3$).

References

1 T.-L. Ho, *Symmetry: A Basis for Synthesis Design*, Wiley, New York, 1995; R. S. Ward, *Chem. Soc. Rev.*, 1990, **19**, 1.
2 D. M. Hodgson, J. Witherington and B. A. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1543; Review: P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, 1991, **2**, 1.
3 J. K. Crandall and M. Apparu, *Org. React. (N.Y.)*, 1983, **29**, 345.
4 R. K. Boeckman Jr., *Tetrahedron Lett.*, 1977, 4281.
5 (*a*) D. Hoppe, F. Hintze and P. Tebben, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1422; (*b*) Review: D. Hoppe, F. Hintze, P. Tebben, M. Paetow, H. Ahrens, J. Schwerdtfeger, P. Sommerfeld, J. Haller, W. Guarnieri, S. Kolczewski, T. Hense and I. Hoppe, *Pure Appl. Chem.*, 1994, **66**, 1479.
6 P. Beak, S. T. Kerrick, S. Wu and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231.
7 H. Gilman, F. W. Moore and O. Baine, *J. Am. Chem. Soc.*, 1941, **63**, 2479; H. Gilman, W. Langham and F. W. Moore, *J. Am. Chem. Soc.*, 1940, **62**, 2327.
8 D. J. Gallagher, S. T. Kerrick and P. Beak, *J. Am. Chem. Soc.*, 1992, **114**, 5872.
9 K. J. Shea and J.-S. Kim, *J. Am. Chem. Soc.*, 1992, **114**, 3044.
10 J. K. Whitesell, M. A. Minton and S. W. Felman, *J. Org. Chem.*, 1983, **48**, 2193.
11 C. Djerassi and J. Staunton, *J. Am. Chem. Soc.*, 1961, **83**, 736.
12 D. I. Schuster, J. Woning, N. A. Kaprinidis, Y. Pan, B. Cai, M. Barra and C. A. Rhodes, *J. Am. Chem. Soc.*, 1992, **114**, 7029.

Received, 13th February 1996; Com. 6/01028H