Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 14, pp. 2303–2306, 1997

Printed in Great Britain
PII: S0957-4166(97)00262-0
0957-4166/97 $17.00 + 0.00

Ligand effects in the organolithium-mediated enantioselective α-deprotonation of achiral epoxides

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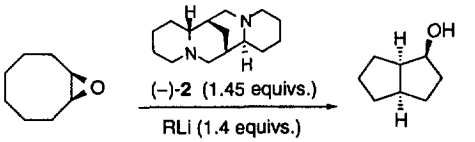
Abstract: The enantioselective α-deprotonation-rearrangement of achiral epoxides using organolithiums with C_2-symmetric ligands [bisoxazolines **4a–d** and (−)-α-isosparteine **5**] is described. © 1997 Elsevier Science Ltd

We recently reported the α-deprotonation-rearrangement of medium-sized (8-, 9- and 10-membered) cycloalkene-derived achiral epoxides using organolithiums in the presence of the commercially available tetracyclic lupine alkaloid (−)-sparteine **2**, which gives bicyclic alcohols in good yields and *ee*s; the predominant sense of asymmetric induction arises from selective removal of the *pro-R* hydrogen on the epoxide ring (eg. Eq. 1).[1] However, as (+)-sparteine[2] is not as readily available as (−)-sparteine **2**, most sparteine-based methods for asymmetric induction do not allow easy conversion of an achiral substrate into either enantiomer of a chiral product.[3] Also, modification/simplification of the sparteine skeleton to improve *ee*s (if required), and/or to attempt to evaluate the factors which influence enantioselectivity, is a major challenge.[4]



R = Bu^s: 70% *ee* (−78 °C), 73% *ee* (−98 °C)
R = Pr^i: 78% *ee* (−78 °C), 83% *ee* (−98 °C) (1)

Although (−)-sparteine **2** is not quite C_2-symmetric, it could be considered as functioning like a C_2-symmetric ligand.[5] For example, interchanging the alkyl group of the organolithium and the epoxide in models of our suggested transition state for epoxide asymmetric α-deprotonation[1b] also results in the *R*-epoxide stereocentre being positioned closest to the lithium–carbon bond. C_2-Symmetric bisoxazolines **4** have been widely used as ligands in asymmetric synthesis and their substituents R_1 and R_2 are easily varied depending on the precursor amino acid/alcohol and substituted malonic acid used.[6] Denmark and co-workers recently reported the use of bisoxazolines **4a–c** [as well as (−)-sparteine **2**] as effective ligands to induce selectivity between enantiotopic faces of imines in the addition of organolithiums.[7] Denmark's work led us to examine whether such ligands might also be able to induce selectivity between enantiotopic hydrogen atoms in the α-deprotonation of epoxides such as **1** using organolithiums (Table 1, the ratios of reagents used are the same as indicated in Eq. 1).

Although the diethyl- and diisobutyl-substituted *tert*-leucine-derived ligands **4a** and **4b** respectively gave some of the highest *ee*s in Denmark's study, they proved unsatisfactory with Bu^{s}Li and epoxide **1**, giving alcohol (+)-**3** in low *ee*s (Table 1, entries 1 and 2). These results could indicate that the *tert*-butyl groups of ligands **4a,b** impede efficient coordination of the epoxide **1** [unlike (planar) imines] in an organolithium–ligand complex. However, we were delighted to find that use of the analogous valine-derived ligands **4c,d** with Bu^{s}Li and epoxide **1** gave alcohol (+)-**3**[8] in 55% *ee* and 66% *ee* respectively (entries 3 and 4). The improved *ee* observed with Bu^{s}Li when using ligand **4d** compared with **4c** might be due to a greater preference for the reaction to proceed *via* aggregates in which the

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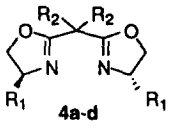
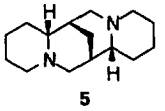
Table 1. Yields and *ees* of alcohol (+)-3 from epoxide 1 using bisoxazolines 4a–d



4a-d

Entry	Ligand	Base	T/ °C[9]	Yield[10]	*Ee*[11]
1	**4a** (R_1 = Bu^t, R_2 = Et)	Bu^{s}Li	−78 to 25	28%	14%
2	**4b** (R_1 = Bu^t, R_2 = Bu^i)	Bu^{s}Li	−78 to 25	38%	3%
3	**4c** (R_1 = Pr^i, R_2 = Et)	Bu^{s}Li	−78 to 25	61%	55%
4	**4d** (R_1 = Pr^i, R_2 = Bu^i)	Bu^{s}Li	−78 to 25	66%	66%
5	**4d** (R_1 = Pr^i, R_2 = Bu^i)	Pr^{i}Li	−78 to 25	65%	60%

Table 2. Yields and *ees* of alcohol (−)-3 from epoxide 1 using (−)-α-isosparteine 5



5

Entry	5 (equivs.)	Base	T/ °C[9]	Yield[10]	*Ee*[11]
1	1.45	Bu^{s}Li	−78 to 25	77%	76%
2	1.45	Pr^{i}Li	−78 to 25	92%	81%
3	1.45	Bu^{s}Li	−98 to 25	72%	72%
4	1.45	Pr^{i}Li	−98 to 25	55%	77%
5	0.5	Pr^{i}Li	−98 to 25	44%	84%
6	0.2	Pr^{i}Li	−98 to 25	86%	84%
7	0.1	Pr^{i}Li	−98 to 25	78%	80%
8	0.01	Pr^{i}Li	−98 to 25	71%	69%

epoxide **1** is oriented so as to place its methylene groups away from the sterically more demanding diisobutyl-substituted bisoxazoline bridge of ligand **4d**. The combination of ligand **4d** with Pr^{i}Li instead of Bu^{s}Li gave alcohol (+)-**3** in slightly lower *ee* (60%, entry 5); this is in contrast to our earlier studies using (−)-sparteine **2** (Eq. 1).

The C_2-symmetric lupine alkaloid (−)-α-isosparteine **5** was first investigated by Zschage and Hoppe in 1992 as an alternative to (−)-sparteine **2** as a chiral ligand in the BuLi-mediated deprotonation of an allylic carbamate where, following transmetallation with Ti(OPr^i)$_4$ and reaction with butanal, it induced 16% *ee* [(−)-sparteine **2** gave 31% *ee*] in the resultant homoallylic alcohol.[12] More recently, Kang and co-workers have reported (−)-α-isosparteine **5** as a superior ligand to (−)-sparteine **2** in several asymmetric transformations: [2,3]-Wittig rearrangements *via* enantioselective deprotonation using Bu^{s}Li in hexane,[13] as well as in Pd-catalysed allylic alkylations and addition of 2-lithio-1,3-dithiane to aldehydes.[14] In contrast, Beak and co-workers found (−)-α-isosparteine **5** to be a poor ligand for enantioselective deprotonation of *N*-Boc pyrrolidine using Bu^{s}Li in ether [10% yield and 61% *ee*, compared with 87% yield and 96% *ee* using (−)-sparteine **2**].[4]

In the present study, reactions of epoxide **1** with Bu^{s}Li and with Pr^{i}Li starting at −78°C in the presence of (−)-α-isosparteine **5** [prepared by $AlCl_3$-promoted isomerisation of (−)-sparteine **2**[15] and dried as a solution in ether over CaH_2 prior to use[13]] gave improved *ees* of (−)-alcohol **3** (76% and 81% respectively, Table 2, entries 1 and 2), when compared with the analogous reactions using (−)-sparteine **2** (70% *ee* and 78% *ee* respectively, Eq. 1). In contrast, for the enantioselective rearrangement of *cis*-cyclodecene oxide to (−)-*endo cis*-1-decalol[1a] using Bu^{s}Li starting at −78°C (−)-sparteine **2** was found to be a more effective ligand than (−)-α-isosparteine **5** (71% yield, 51% *ee*, and 83% yield, 38% *ee* respectively). On commencing reactions of epoxide **1** with (−)-α-isosparteine **5** at −98°C slightly lower enantioselectivities were observed than at −78°C (compare entries 3 and 4 with 1 and 2), which may be due to the partially heterogeneous nature of these particular reaction mixtures at −98°C.

We had previously found that for the reaction of epoxide **1** with Bu^{s}Li starting at −98°C it was possible to reduce the quantity of (−)-sparteine **2** and still achieve asymmetric induction, although *ees*

of, and conversions to, (−)-alcohol **3** were reduced in these cases {using **2** (0.5 and 0.2 equivs. relative to **1**) gave **3** [58% yield (73% based on recovered **1**), 69% *ee*, and 53% yield (76% based on recovered **1**), 55% *ee* respectively]}.[1a] The combination of 0.2 equiv. of (−)-sparteine **2** with Pr^iLi starting at −98°C[9] gave (−)-alcohol **3** in good *ee* (62% yield, 73% *ee*) and even using only 0.01 equivs. of (−)-sparteine **2** in the reaction of epoxide **1** with Pr^iLi at −98°C[9] gave moderately enantioenriched (−)-alcohol **3** (65% yield, 31% *ee*). However, the gradual erosion in *ee* on reducing the proportion of the chiral ligand with either Bu^sLi or Pr^iLi suggests that (−)-sparteine **2** does not function efficiently as a catalyst at −98°C.[16] In comparison (−)-α-isosparteine **5** is much more effective as a catalyst for enantioselective deprotonation of epoxide **1** (Table 2, entries 5, 6, 7 and 8; the reaction mixtures were homogeneous in these cases). Beak has speculated that the reduced reactivity of (−)-α-isosparteine **5** compared with (−)-sparteine **2** in the enantioselective deprotonation of *N*-Boc pyrrolidine could be due to the Bu^sLi–ligand complex being more sterically hindered in the case of (−)-α-isosparteine **5** (due to both peripheral rings extending towards the organolithium).[4] In the present case with epoxide **1**, the rate of deprotonation does not seem to be significantly altered when using (−)-α-isosparteine **5** instead of (−)-sparteine **2** (Table 2, entries 1–4),[16] and additional steric hindrance in the complex formed between (−)-α-isosparteine **5** and the lithium alkoxide of alcohol **3** following deprotonation-rearrangement may aid dissociation of the ligand and thus promote catalysis.

In summary, we have shown that bisoxazolines **4a–d** can be used as ligands to induce enantioselective deprotonation although, at present, the *ees* obtained with epoxide **1** are lower than when using (−)-sparteine **2** or (−)-α-isosparteine **5** as the ligand. However, the advantages of using bisoxazolines when compared with using the sparteines are the ability to modify the bisoxazoline substituents to enhance *ee* and straightforward access to either enantiomer of a chiral product from an achiral substrate. The observation of significant asymmetric induction when using as little as 1 mol% (−)-α-isosparteine **5** is encouraging for the further development of catalytic asymmetric processes using nitrogen donor ligands with organolithiums.

Acknowledgements

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 The Royal Society for a Research Grant towards a HPLC system, the EPSRC Mass Spectrometry Service Centre for mass spectra, Zeneca (Strategic Research Fund) and Pfizer for additional financial support, and Prof. D. Hoppe and K. Behrens for additional details concerning the synthesis of (−)-α-isosparteine **5**.

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2. (+)-Sparteine can be obtained, for example, by reduction of (−)-lupanine (2-oxosparteine) obtained by resolution of the racemate obtained from *Lupinus albus L.* (Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm. (Weinheim)* **1989**, *322*, 399–403).
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8. In contrast to our results, in the addition of organolithiums to imines[7] bisoxazoline ligands **4a–c** gave the same sense of asymmetric induction as (−)-sparteine **2**.

9. The reaction mixtures were maintained at −78°C or −98°C for 5 h following addition of the epoxide and then warmed slowly to ambient temperature overnight. For the general experimental protocol followed see reference 1a.
10. Isolated total yields of chromatographically homogeneous, spectroscopically pure products are reported [except for entries 4 and 5 in Table 1 where alcohol **3** co-eluted with *ca* 10 mol% of bisoxazoline **4d** on column chromatography (Et_2O, SiO_2) and the yields reported for these two reactions are based on the amounts of alcohol **3** present in the mixtures by ^1H NMR analysis].
11. *Ee*s were determined by HPLC.[1a]
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16. In the absence of (−)-sparteine **2** no reaction was observed between epoxide **1** and either Bu^sLi or Pr^iLi at −98°C for 5 h. At −78°C for 5 h both Bu^sLi and Pr^iLi gave some alcohol **3** {38% [5% after 10 min (following complete addition of the epoxide **1**)][1a] and 11% respectively}; we had previously established that the reaction between epoxide **1** and Bu^sLi in the presence of (−)-sparteine **2** was essentially complete after 5 h at −78°C[1a] [75%, 36% conversion to (−)-alcohol **3** was observed after 10 min (following complete addition of the epoxide **1**)]. There was no change in the *ee* of (−)-alcohol **3** during the course of the latter reaction suggesting that the gradual generation of the lithium alkoxide of (−)-alcohol **3** does not influence the asymmetric induction (chiral alkoxides can effect enantioselective deprotonations: Amadji, M.; Vadecard, J.; Plaquevent, J.-C.; Duhamel, L.; Duhamel, P. *J. Am. Chem. Soc.* **1996**, *118*, 12483–12484, and references cited therein).

(Received in UK 27 May 1997)