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A new and enantioselective indolizidine synthesis by *meso*-epoxide α-deprotonation–transannular N–C insertion

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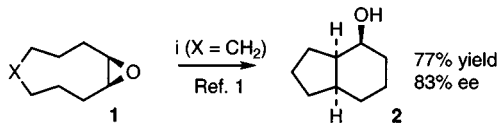
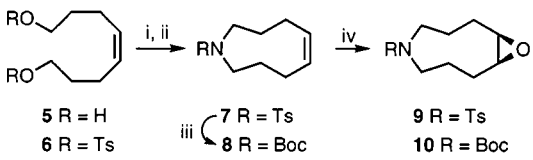
Enantioselective α-deprotonation–rearrangement of *N*-Boc hexahydroazonine oxide 10 using organolithiums in the presence of (-)-sparteine 3 gives the ester 12 in up to 89% ee.

We recently reported the enantioselective α-deprotonation–rearrangement of medium-sized (8-, 9- and 10-membered) cycloalkene-derived achiral epoxides using a secondary organolithium in combination with a chiral ligand such as (−)-sparteine **3**, which gives bicyclic alcohols in good yields and ees (77–84% ee, *e.g.* Scheme 1, X = CH_2).[1] However, only a single functional group is generated in the desymmetrised bicycles. One strategy to enhance the utility of this transformation would be to examine heterocycloalkene-derived achiral epoxides. Here we communicate our preliminary results concerning the synthesis and novel rearrangement chemistry of an azacyclic epoxide of this type (**1**, X = NR).



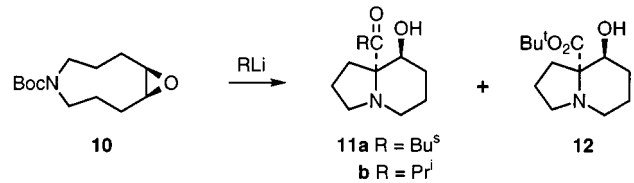
Scheme 1 *Reagents and conditions*: i, Pr^iLi (2.4 equiv.), (−)-sparteine **3** (2.5 equiv.), Et_2O, −98 °C (5 h) to 25 °C (15 h).

An important aspect of the study of transannular reactions of a medium-sized heterocycle concerns the potential problem of preparing the substrate.[2] However, application of methodology[3] used in the synthesis of the azacycloundecene system found in manzamine C led to a highly satisfactory route to the azacyclic epoxide **9** (Scheme 2). Thus, cyclisation under dilute conditions of the ditosylate **6** of the known diol **5** (readily available from cycloocta-1,5-diene)[4] gave the reduced azonine **7** in 62% yield; to the best of our knowledge this is the most efficient cyclisation reported which gives a simple reduced azonine.[2]



Scheme 2 *Reagents and conditions*: i, TsCl (4.9 equiv.), Py, 0 °C (5 h) to 25 °C (15 h), 74%; ii, $TsNH_2$ (1.7 equiv), NaOH (200 equiv.), Bu_4NI (1.4 equiv.), toluene–H_2O, reflux, 5 h, 62%; iii, Na naphthalenide (2.5 equiv.), THF, −78 °C, then HCl(g), then Et_3N (1.5 equiv.), Boc_2O (1.5 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, 25 °C, 64% from **7**; iv, $MeCO_3H$ (1.2 equiv.), Na_2CO_3 (3 equiv.), NaOAc (0.02 equiv.), CH_2Cl_2, 0 °C (10 min) to 25 °C (15 h), 82% (R = Ts), 87% (R = Boc).

Subjection of the epoxide **9**, derived from reduced azonine **7**, to typical asymmetric rearrangement conditions[1] [Bu^sLi (2.4 equiv.) and (−)-sparteine **3** (2.5 equiv.) in Et_2O at −78 °C for 5 h, followed by warming to 25 °C over 15 h, *cf.* Scheme 1] led only to the recovery of starting epoxide **9**, whereas quenching the reaction with D_2O led to essentially complete *o*-deuterium incorporation into the tosyl group of the recovered starting material (64%). An attempt to induce reaction at the epoxide group subsequent to *ortho*-deprotonation using double the quantities of reagents indicated above led to no identifiable products; an alternative protecting group was therefore required. Removal of the tosyl group from **7** using sodium naphthalenide and immediate Boc reprotection of the amine hydrochloride salt gave the reduced azonine **8** (64%). Epoxidation provided **10**, which could potentially undergo deprotonation with an organolithium either α to the epoxide oxygen, or α to nitrogen. Beak has reported a 6-*exo-tet* cyclisation onto an epoxide *via* deprotonation α to NBoc; the deprotonation site was however also benzylic in this case.[5] Beak has also reported that the rate of deprotonation of Boc-protected azacycles decreases on moving from pyrrolidine to piperidine to perhydroazepine.[6] In the event, reaction of the epoxide **10** with Bu^sLi (2.4 equiv. in Et_2O at −78 °C for 5 h, followed by warming to 25 °C over 15 h) led to an inseparable 1 : 1 mixture of epimers (due to the stereogenic centre in the Bu^s group, *vide infra*) of ketone **11a** (48%, 70% based on recovered epoxide **10**, Scheme 3).



Scheme 3

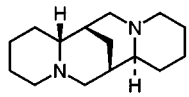
In contrast, reaction of the epoxide **10** with Bu^sLi, under the same conditions but in the presence of TMEDA (2.5 equiv.), led to the formation of ester **12** as the major product (**12** : **11a**, 8 : 1 by ^1H NMR analysis; 74% isolated yield of **12**). Using (−)-sparteine **3** as the ligand in an otherwise identical experiment gave an equal mixture of **11a** and **12** (66% ee for **12**).† Experiments were then carried out to examine the possibility of increasing both the proportion and ee of ester **12** formed from epoxide **10** (Table 1).

Maintaining the reaction at −78 °C for 18 h and then quenching at this temperature gave ester **12** in improved ee (74%, Table 1, entry 1), but the ketone **11a** predominated. However, repeating the same procedure at −98 °C significantly improved the proportion of ester **12** (**12** : **11a**, 5 : 1) and increased the ee of **12** to 79% (entry 2). Using Pr^iLi at −98 °C gave mainly the ester **12** (**12** : **11a**, 10 : 1) and with the highest level of asymmetric induction (89% ee, entry 3),‡ as also observed with our earlier work on cycloalkene-derived epoxides.[1] Using (−)-α-isosparteine **4** as ligand with either Bu^sLi or Pr^iLi slowed the reaction considerably (entries 4 and 5), particularly in conjunction with Bu^sLi; the ees were also reduced compared with the corresponding (−)-sparteine **3** reactions. In an attempt to allow Pr^iLi/(−)-α-isosparteine **4** to completely consume the epoxide **10**, the reaction was left for 40 h at −98 °C (entry 6), but it still remained only 50% complete after this time and no change in the ee of ester **12** was observed. The use of catalytic amounts of ligand was also investigated

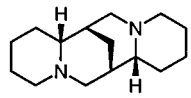
Table 1 Effect of experimental conditions on the yields and enantioselectivities of formation of indolizidine **12** from epoxide **10** using ligand/RLi in Et_2O

Entry[a]	Ligand	RLi	**10** : **11** : **12**[b]	Yield of **12**[c] (%)	Ee of **12** (%)
1[d]	**3**	Bu^{s}Li	0 : 1.6 : 1.0	32 (20)	74
2	**3**	Bu^{s}Li	0.1 : 0.2 : 1.0	58 (50)	79
3	**3**	Pr^{i}Li	0.3 : 0.1 : 1.0	57 (49)	89
4	**4**	Bu^{s}Li	5.0 : 0 : 1.0	14	64
5	**4**	Pr^{i}Li	2.0 : 0.1 : 1.0	29	79
6[e]	**4**	Pr^{i}Li	1.3 : 0.1 : 1.0	40	78
7[f]	**3**	Pr^{i}Li	0.7 : 0.6 : 1.0	36	82
8[f]	**4**	Pr^{i}Li	1.2 : 0.1 : 1.0	33	77
9[e,f]	**4**	Pr^{i}Li	0.4 : 0.2 : 1.0	54	89

[a] Ratio of ligand : RLi : epoxide **10**, 2.45 : 2.4 : 1 and carried out at −98 °C with a reaction time of 18 h unless otherwise indicated. [b] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of **12** as measured by ^{1}H NMR analysis using methyl diphenylacetate as an internal standard. Isolated yields given in parentheses. [d] Carried out at −78 °C. [e] Reaction time 40 h. [f] Ratio of ligand : RLi : epoxide **10**, 0.24 : 2.4 : 1.



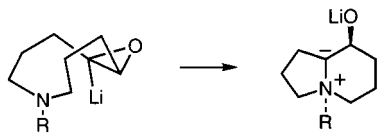
(−)-**3**



(−)-**4**

(entries 7–9) with interesting results. Using 24 mol% (−)-sparteine **3** (10 mol% with respect to Pr^{i}Li), high levels of ee (82%) were still achieved, but the reaction was found to be much slower. In contrast, (−)-α-isosparteine **4** was more effective when used in a catalytic fashion (entry 8), with no apparent change in the ee (compare entry 5). Repeating this last reaction but leaving it for 40 h at −98 °C allowed the reaction to proceed further to completion and also gave a much higher level of ee (entry 9).

The structures of indolizidinols **11** and **12** were assigned by extensive spectroscopic investigations and were later further supported by X-ray crystallographic analysis of ketone **11b**.§ A mechanistic explanation for the formation of the indolizidinols is that they arise *via* lithiation α to the epoxide oxygen to give **13**, followed by transannular reaction using the N lone pair to give an ammonium ylide **14** which undergoes [1,2] migration of the exocyclic N substituent (Scheme 4); direct insertion of the lithiated epoxide into the exocyclic C–N bond is also possible. Incorporation of the organolithium to give the ketones **11** could occur before or after the transannular reaction. The latter



13 **14**

Scheme 4

process seems most likely, since reducing the equivalents of organolithium from 2.5 improves (at the expense of conversion of starting epoxide **10**) the ratio of ester **12** : ketone **11**, and in a separate experiment ester **12** could be quantitatively converted to ketone **11b** using Pr^{i}Li (1.1 equiv., −78 °C for 1 h, followed by warming to 0 °C over 2 h).

Insertion of a lithiated epoxide into a C–N bond has not previously been reported and the present study illustrates an example of this process leading to a new and enantioselective entry to the important indolizidine framework. Further studies on the scope of this process are in progress and will be reported in due course.

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Notes and references

† Ees were determined by GC (Chrompack chirasil-dex 25 m × 0.32 mm ID column; 6 psi, 120 °C). The absolute configurations of the predominant indolizidinol enantiomers are not known but can be tentatively assigned as shown in Scheme 3 by analogy with the selectivity for deprotonation at the *R* configured epoxide stereocentre with (−)-sparteine **3** observed in our earlier medium-ring studies (ref. 1).

‡ Freshly distilled (−)-sparteine (70 mm^3, 0.30 mmol) in Et_2O (1 cm^3) was added dropwise over 0.5 h to a stirred solution of Pr^{i}Li [1.09 mol dm^{-3} in light petroleum (boiling range 40–60 °C); 270 mm^3, 0.29 mmol] in Et_2O (1 cm^3) at −98 °C. The reaction mixture was allowed to stir for 1 h at −98 °C before the epoxide **10** (30 mg, 0.12 mmol) in Et_2O (1 cm^3) was added dropwise over 0.5 h. The reaction mixture was stirred for 18 h at this temperature and then H_3PO_4 (0.5 mol dm^{-3} in water; 1 cm^3) added slowly dropwise. After warming to room temperature the organic layer was removed and the aqueous layer extracted with Et_2O (3 × 5 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated under reduced pressure. Purification of the residue by column chromatography [(SiO_2, 50% Et_2O–light petroleum (boiling range 40–60 °C) → 100% Et_2O] gave the ester **12** (14.8 mg, 49%); $[\alpha]_D^{21}$+48.6 (*c* 0.3 in $CHCl_3$).

§ *Crystal data* for **11b**: $C_{12}H_{20}NO_2$, *M* = 210.29, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 5.807(7), *b* = 13.393(2), *c* = 15.477(3) Å, *V* = 1203.7(3) Å^3, *Z* = 4. 1038 independent reflections measured at 173 K on an Enraf-Nonius DIP2000 diffractometer. Mo-Kα radiation. 718 reflections with $I > 8\sigma(I)$ and 137 variables yield R = 0.064, R_w = 0.063. CCDC 182/1138. Crystal data are available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/309/

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