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Enantioselective synthesis of epoxides by α-deprotonation—electrophile trapping of achiral epoxides

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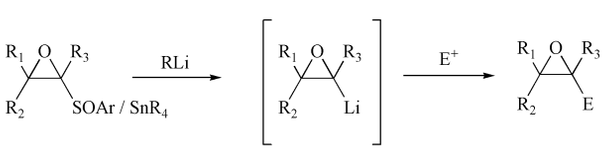
Enantioselective α-deprotonation of achiral epoxides **1**, **21**, and **26** using organolithiums in the presence of (−)-sparteine **2** and subsequent electrophile trapping gives access to enantioenriched trisubstituted epoxides **9**–**17**, **22**, **23**, **27** and **28** (in up to 86% ee).

Introduction

The enantioselective desymmetrisation of an achiral compound is an attractive and powerful concept;[1] its application to *meso*-epoxides has been developed in a number of ways,[2–8] yet in these approaches the epoxide functionality is removed in an enantioselective chemical transformation. As epoxides are widely found both as versatile synthetic intermediates, and in a number of interesting natural products,[9] the development of efficient (especially asymmetric) methods for the elaboration of epoxides constitutes an important ongoing challenge.[10,11] Such a strategy could use the nucleophilic chemistry of epoxides (*via* oxiranyl anions),[4] first studied by Eisch and Galle,[12] which is far less developed than the use of epoxides as electrophiles. A current requirement with this latter strategy is that, in order to avoid any subsequent rearrangement of the reactive α-metallated epoxide,[4,5] the epoxide must possess an activating substituent (electron-withdrawing, trialkylsilyl, or trialkylstannyl group) attached to the epoxide ring. Electron-withdrawing and trialkylsilyl substituents facilitate formation of oxiranyl anions by promoting deprotonation (usually lithiation) and prolonging the solution lifetime of these otherwise very labile intermediates. Trialkylstannyl- and sulfinyl-substituted epoxides react with organolithiums (by transmetallation and desulfinylation, respectively, Scheme 1)[13,14] rapidly enough at low temperatures such that the resultant unstabilised oxiranyl anions can exhibit synthetically useful nucleophilic (rather than carbene-type) reactivity with a range of electrophiles.

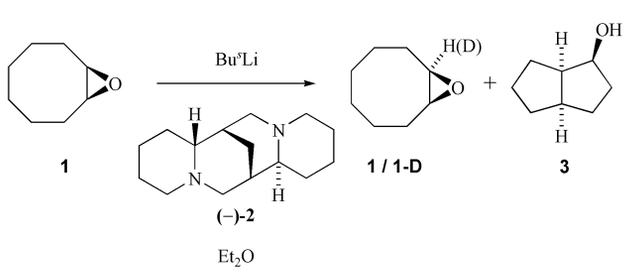


Scheme 1

Such reactions demonstrate the value of oxiranyllithiums as important intermediates in the elaboration of epoxides. However, they also indicate the potential limitation of requiring an activated epoxide precursor to carry out the chemistry. Recently, we showed that conservation of epoxide functionality was possible after direct lithiation of terminal epoxides in the presence of a diamine ligand, followed by electrophile trapping of the non-stabilised oxiranyl anion intermediates.[15] However, the reaction was restricted to silylation (TMSCl present during generation of the oxiranyl anion) and deuteration (CD_3OD as external electrophile). We have also recently communicated that a similar strategy could be used to enantioselectively desymmetrise epoxides of cycloalkenes and report here our studies in detail.[16]

Results and discussion

As previously observed during our studies on enantioselective α-lithiation–rearrangement of *meso*-epoxides of medium-sized cycloalkenes (*e.g.* **1**⟶**3**, Scheme 2), rearrangement occurs efficiently upon warming of the reaction mixture from −90 °C in Et_2O.[17] Therefore, in order to trap the transient oxiranyl anion, we carefully explored the time required for its formation at −90 °C by quenching the reaction at increasing duration with CD_3OD. The initial reaction conditions used [Bu^sLi (2.45 equiv.), (−)-sparteine **2** (2.5 equiv.), Et_2O, −90 °C] were the same as those for the rearrangement of (commercially available) cyclooctene oxide **1** (Scheme 2).[17] As only two compounds (starting material and bicyclic alcohol **3** from transannular rearrangement) were observed by TLC, the % D incorporation in **1** was determined from the crude ^1H NMR spectrum of the reaction mixture after aqueous work-up. These results showed a significant increase in D incorporation over the first 20 minutes (Table 1). It is noteworthy that the amount of **3** increased at a slower rate, with it mainly arising between 5 and 10 minutes after addition of the epoxide **1** to the Bu^sLi–**2** mixture. Once α-lithiation is complete, the lithiated epoxide is surprisingly stable towards transannular C–H insertion with no decomposition observed over a 2 h period; some reaction was observed over 14 h, however (Table 1, entry 7). These results indicate that the initial formation of **3** occurs during the deprotonation, possibly due to local heating in the likely exothermic lithiation. From the crude ^1H NMR spectra, only cyclooctene oxide **1/1-D** and bicyclic alcohol **3** were present after aqueous work-up. Also of interest is the observation of complete rearrangement to the bicyclic alcohol **3** after 3 h when the deuteration was attempted with D_2O rather than CD_3OD,



Scheme 2

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Table 1 Reaction profile as a function of time using epoxide **1** with Bu^{s}Li (2.45 equiv.) and (−)-sparteine **2** (2.5 equiv.) in Et_2O at −90 °C, followed by the addition of CD_3OD after the time indicated

Entry	Reaction time	% D incorporation in **1** [a]	Isolated yield of **3** (%)
1	5 min	40	Traces
2	10 min	56	26
3	15 min	63	19
4 [b]	20 min	100	29
5	30 min	100	29
6	2 h 30 min	100	28
7	14 h	100	43

[a] Crude ^{1}H NMR spectra and GC analysis only show the presence of **1/1-D** and **3**. [b] Cyclooctene oxide **1-D** was isolated in 61% yield.

Table 2 Reaction profile as a function of time using epoxide **1** with Bu^{s}Li (1.25 equiv.) and (−)-sparteine **2** (1.3 equiv.) in Et_2O at −90 °C

Entry	Reaction time	% D incorporation in **1**	Isolated yield of **3** (%)
1	30 min	78	0
2 [a]	1 h	100	3
3	1.5 h	100	5.5
4	2 h	100	10
5	14 h	100	17

[a] Cyclooctene oxide **1-D** was isolated in 85% yield.

Table 3 Reaction profile as a function of time using epoxide **1** with Bu^{s}Li (1.25 equiv.) and TMEDA (1.3 equiv.) in Et_2O at −90 °C

Entry	Reaction time	% D incorporation in **1**	Isolated yield of **3** (%)
1	30 min	49	0
2	2 h	84	0
3	3 h	98	Traces
4	14 h	100	20

probably because of a miscibility issue combined with a lack of temperature control due to localised heating while quenching with D_2O.

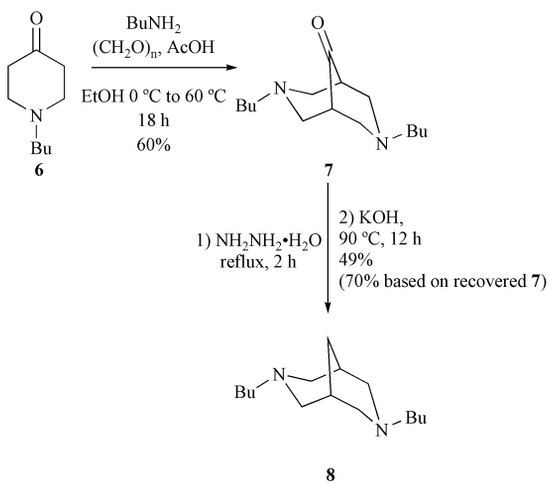
With the nucleophilic (or strictly in this case, basic) nature of the transient lithiated epoxide established, we tried to optimise the efficiency of the reaction by accelerating the trapping reaction and at the same time limiting the rate of the rearrangement. The first objective could potentially be achieved by the addition of a more polar co-solvent after generation the oxiranyl anion. This was attempted by producing the oxiranyl anion under the above conditions and then after 20 min adding pre-cooled THF (1 ml when 10 ml Et_2O had been used) at −90 °C and leaving for a further 5 min before quenching with CD_3OD. This reaction clearly showed the high destabilising effect of THF on the oxiranyl anion, since the bicyclic alcohol **3** was now obtained in 64% yield. This effect could be due to displacement of the (−)-sparteine **2** ligand around the lithium of the lithiated epoxide by THF [15,18] and would support the hypothesis that the (−)-sparteine **2** is stabilising the lithiated oxiranyl anion. Moreover, only 30% yield of cyclooctene oxide **1** was obtained, with only 43% D incorporation. This poor yield and D incorporation rules out the use of a polar co-solvent. We then investigated the influence of the presence of the diamine ligand on the formation and potential stabilisation of the oxiranyl anion. It was found that after stirring for 1 h without (−)-sparteine **2** under otherwise identical conditions, only 30% of the recovered cyclooctene oxide **1** was deuterated and also the reaction yielded 12% of bicyclic alcohol **3**. This result demonstrates that the presence of (−)-sparteine **2** not only facilitates the deprotonation of cyclooctene oxide **1** but also helps to achieve a better ratio **1-D** : **3**, this ratio being lowered from 5 : 1 with (−)-sparteine **2** to 2 : 1 without diamine. This also indicates that there is likely to be a modification of the aggregate of the lithiated epoxide in the presence of a diamine ligand (as has been clearly established for alkyllithiums).[19] Finally, we examined the quantity of alkyllithium and (−)-sparteine **2** required to allow complete deprotonation. Deuteration experiments were carried out with reactions involving Bu^{s}Li (1.25 equiv.) and (−)-sparteine **2** (1.3 equiv.). The results obtained as a function of the reaction time are given in Table 2.

Not surprisingly, comparison of the results in Tables 1 and 2 show that using a lower quantity of base leads to a lower rate of deprotonation of cyclooctene oxide **1**. After 30 min, the deuteration is not complete (Table 2, entry 1), this contrasts with the case using 2.45 equiv. of Bu^{s}Li (Table 1, entries 4 and 5). However, the most interesting observation is the reduced amount of bicyclic alcohol **3** obtained under the conditions reported in Table 2. Indeed, when using 2.45 equiv. of Bu^{s}Li at least 20% of **3** was obtained, together with fully deuterated **1-D** (Table 1); with the smaller excess of alkyllithium only trace amounts of **3** are obtained after 1 h (Table 2, entry 2). The slower rate of deprotonation (leading to less localised heating) and/or aggregate modification (due to the lower quantity of Bu^{s}Li present) may be the origin of the reduced quantity of bicyclic alcohol **3** formed.

The results shown in Table 2 are significant since not only do they indicate a lower quantity of organolithium can be used, but they also permit the use of a smaller excess of electrophile, resulting in fewer by-products. As the products obtained by extension of this methodology to the trapping of electrophiles other than D^+ would give enantioenriched products, for which the determination of the ee would be important, we then sought a way to access racemic samples for ee determinations. We first examined the use of TMEDA as an achiral additive. The first requirement was to establish the reaction time necessary to fully lithiate cyclooctene oxide **1** using Bu^{s}Li (1.25 equiv.) with TMEDA (1.3 equiv.) in Et_2O at −90 °C. The results obtained after quenching with CD_3OD are summarised in Table 3. It is noteworthy that after 3 h almost complete D incorporation was achieved and only traces of bicyclic alcohol **3** was detected in the crude ^{1}H NMR spectrum.

We then sought to probe the effect of the structure of the achiral diamine on the reaction profile. In order to mimic more closely the structure of (−)-sparteine **2** we decided to use

3,7-dibutyl-3,7-diazabicyclo[3.3.1]nonane **8** (also called dibutylbispidine, DBB). This bicyclic diamine is classically obtained *via* a Wolff–Kishner reduction of bispidinone **7**, which itself arises from a double Mannich reaction with 4-butylpiperidone **6** (Scheme 3).[20–22] We, and others,[23] have found difficulties in this synthetic route to 3,7-dialkylbispidines, mainly due to the harsh conditions required. Our main concern was to reproduce the Wolff–Kishner reduction using anhydrous hydrazine in a steel bomb. We therefore considered alternative ways to reduce the ketone. As Clemmensen reduction failed, we used the Wolff procedure involving the isolation of the intermediate hydrazone (formed in this case by reaction of the bispidinone **7** with an excess of hydrazine monohydrate at reflux) and its subsequent reaction with potassium hydroxide; this procedure proved to be reproducible in our hands allowing after distillation the isolation of 49% of DBB **8** on up to 20 g scale. Also of interest is that refluxing the distillation residue in conc. HCl allowed a partial recovery of the starting bispidinone **7** permitting recycling. The total conversion of bispidinone **7** to bispidine **8** then reaches 70%.

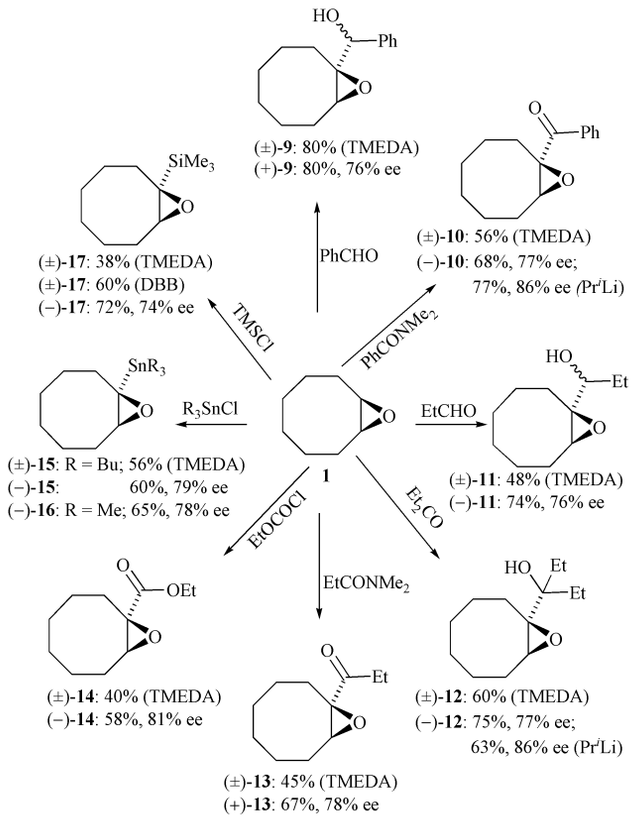


Scheme 3

Having a significant quantity of bispidine **8** in hand, we examined the deuteration of cyclooctene oxide **1** utilising this diamine ligand **8** (1.3 equiv.). The reaction time required to obtain complete D incorporation with epoxide **1** proved much longer than previously observed using (−)-sparteine **2**, indicating a strong dependence of the rate of deprotonation on the structure of the alkyllithium–diamine complex. After 16 h, complete D incorporation was obtained with only 13% of bicyclic alcohol **3** additionally present, indicating a good stability in the presence of **8** of the transient oxiranyl anion with respect to the rearrangement. This product profile is comparable with that obtained with (−)-sparteine **2** and indicates a potential stabilisation of the lithiated epoxide. The stabilisation arising from the presence of (−)-**2** or **8** might be explained either by 'protection' induced by a bulky complex, or by a more important modification of the structure of the aggregate.

We then moved on to examine more useful electrophile trapping reactions that would allow the creation of new carbon–carbon and carbon–heteroatom bonds. Significantly, when using TMEDA (1.3 equiv.) as the ligand with Bu^{s}Li (1.25 equiv.), introduction of a wide array of functionality at the epoxide carbon of cyclooctene oxide **1** was found to be possible using a range of electrophiles (1.5 equiv. unless indicated otherwise) (Scheme 4).

For the electrophile trapping of epoxide **1** using TMEDA as the diamine ligand, the reaction with benzaldehyde yielded the corresponding benzylic alcohol **9** in good yield (80%, 1:1 mixture of chromatographically inseparable diastereoisomers),[24] while the corresponding ketone **10** was obtained *via* reaction



Scheme 4 Electrophile trapping of epoxide **1** using Bu^{s}Li (1.25 equiv. unless indicated otherwise) with TMEDA, DBB **8**, or (for the enantioenriched products) (−)-sparteine **2** (1.3 equiv.).

with *N*,*N*-dimethylbenzamide (56%). Acylation using an amide indicates that the destabilised oxiranyl anion possesses good nucleophilicity toward relatively unreactive electrophiles. Reactions with propanal, 3-pentanone and *N*,*N*-dimethylpropionamide yielded the corresponding alcohols **11** and **12** and ketone **13** (in 48%, 60% and 45% yields, respectively), showing that reaction with potentially enolisable aldehydes, ketones and amides is achievable. It also proved possible to introduce an alkyl group, using MeI to give α-methylcyclooctene oxide **18** (75%). The yield of the latter was determined by GC, as it proved to have the same R_f by TLC as the starting material, which made up the rest of the material. Attempts to trap the anion with other alkyl halides such as butyl iodide and allyl bromide proved to be unsuccessful by this procedure, and the cyclooctene oxide **1** was recovered with no deuterium incorporation after quenching with deuterated methanol. Use of ethyl chloroformate (15 equiv.) allowed isolation of the α,β-epoxyester **14** (40%). α-Tributylstannyl epoxide **15** was obtained (56%) from reaction with Bu_3SnCl. It is noteworthy that using TMEDA in the direct trapping methodology gave important variation in isolated yields: use of TMSCl as an external electrophile resulted in a poor yield of the α,β-epoxysilane **17**. However, when TMSCl was added with the epoxide a 38% yield of **17** could be realised, which improved to 60% using DBB **8**.

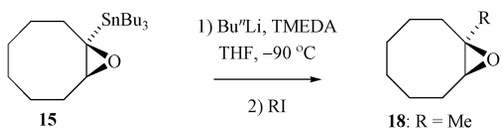
At this point, we examined trapping the transient oxiranyl anion generated in the presence of (−)-sparteine **2** in order to create new enantioenriched products containing carbon–carbon or carbon–heteroatom bonds while retaining the epoxide functionality (Scheme 4). Using the best experimental conditions established for the deuteration of cyclooctene oxide **1**, we examined trapping various electrophiles. We first explored the possibility of creating a carbon-carbon bond in a single step.

Trapping the oxiranyl anion with benzaldehyde gave 80% of the desired epoxyalcohol (+)-**9** as a 2 : 1 mixture of diastereoisomers (by ^{1}H NMR). After MnO_2 oxidation to the ketone (−)-**10**, a 76% ee was measured. Reaction with *N*,*N*-di-

methylbenzamide led to the corresponding ketone (−)-**10** in 68% yield with 77% ee. Using Pr^{i}Li instead of Bu^{s}Li gave a significant increase of the ee of (−)-**10** (86% compared to 77%). This reflects the higher enantiotopic proton selection of Pr^{i}Li–(−)-**2** *vs.* Bu^{s}Li–(−)-**2** with epoxide **1**.[17] Addition to an enolisable aldehyde such as propionaldehyde also proved to be successful. This led to the corresponding epoxyalcohol (−)-**11** in 74% yield but with no diastereomeric excess. Dess–Martin oxidation of epoxyalcohol (−)-**11** to ketone (+)-**13** allowed the ee to be determined (76%). Moving to more bulky carbonyl compounds did not disfavour the reaction. Addition of 3-pentanone gave a 75% yield of the corresponding tertiary alcohol (−)-**12** in 77% ee. Using Pr^{i}Li instead of Bu^{s}Li again allowed a significant increase of the ee of (−)-**12** (up to 86%). Reaction with the corresponding amide, *N*,*N*-dimethylpropionamide led to the corresponding ketone (+)-**13** in 67% yield with 78% ee. We tried then to apply this methodology to the synthesis of trialkyl-substituted epoxides. Trapping the lithiated epoxide with methyl iodide yielded an inseparable mixture of cyclooctene oxide **1** and α-methylcyclooctene oxide **18**. Finally, using a large excess (15 equiv.) of ethyl chloroformate we managed to isolate a reasonable yield (58%) of the epoxyester (−)-**14** in 81% ee. The use of a stoichiometric amount of this electrophile yielded an inseparable 1 : 1 mixture of the epoxyester (−)-**14** and the diepoxyketone resulting from addition of lithiated **1** to **14**. When this reaction was carried out using 3 or 15 equivalents of ethyl chloroformate, none of the diepoxyketone was observed. With 3 equiv. of electrophile, the epoxy ester (−)-**14** was obtained in 51% yield. Alternatively, epoxyester (−)-**14**, could potentially be prepared using ethyl cyanoformate, but this proved unsuccessful and no identifiable products were isolated. Attempts to trap the oxiranyl anion with benzophenone yielded a complex mixture of uncharacterised compounds.

In order to create valuable carbon–heteroatom bonds enantioselectively, we first examined the use of trimethyltin chloride (1.3 equiv.) as the electrophile, which gave epoxystannane (−)-**16** in 65% yield and 78% ee (determined after BuLi-induced transmetallation 3-pentanone trapping). If tributyltin chloride was used then the reaction afforded the corresponding epoxystannane (−)-**15** in similar yield and ee to (−)-**16**. We then turned our attentions to trap the oxiranyl anion with TMSCl as an internal electrophile (*cf.* the trapping using TMEDA as the diamine ligand); this yielded 72% of the silylated epoxide (−)-**17** with 74% ee. This reaction is of significance since α-silylated epoxides are valuable intermediates in organic synthesis.[25] Reactions with a more bulky silane, namely TBDPSCl, were unsuccessful. The fact that similar levels of enantioenrichment were observed for all the electrophiles examined reflects the fact that the enantiodiscriminating event is the deprotonation before the electrophile is added. In the case of TMSCl present *in situ*, the TMSCl does not appear to influence the enantioselectivity of the deprotonation step. The absolute configuration of the predominant enantiomers formed in the enantioselective lithiation–electrophile trappings of epoxide **1** are as shown in Scheme 4, and are assigned from the known sense of asymmetric induction in the deprotonation of epoxide **1** (at the *R*-epoxide stereocentre)–rearrangement to alcohol **3** using (−)-sparteine **2**.[17]

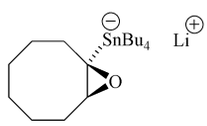
The synthesis of the epoxystannanes may allow incorporation of other electrophiles using subsequent cross-coupling techniques.[26] We have used the stannylated cyclooctene oxide **15** in transmetallation reactions. Pfaltz and co-workers originally reported the tin–lithium exchange of an epoxystannane and subsequent electrophile trapping of the intermediate oxiranyllithium.[13] Using the stannylated epoxide **15** allowed electrophile trapping in a solvent other than Et_2O, and as the generation of the oxiranyl anion is almost instantaneous, the reaction times are considerably reduced. Indeed, running the reaction for 5 min with Bu^{n}Li (1.3 equiv.) and TMEDA (2 equiv.) in THF at −90 °C, followed by addition of MeI allowed the isolation of 72% of the α-methylated epoxide **18** (Scheme 5). It is also noteworthy that this procedure allowed purification of the latter (which was not possible by direct lithiation–trapping). Under the same conditions, it was also possible to trap the lithiated epoxide using butyl iodide, albeit in very low yield (11%).



15 **18**: R = Me **19**: R = Bu

Scheme 5

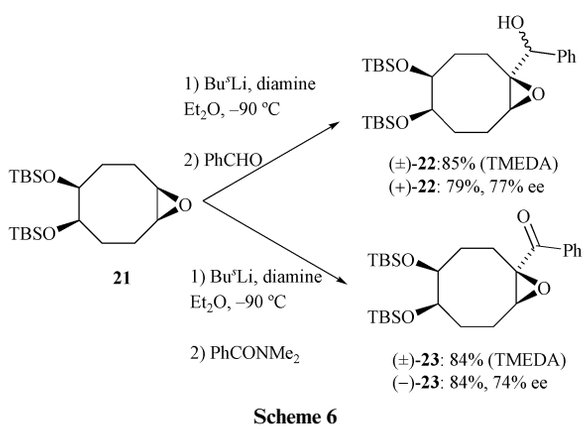
We also examined the possible formation of a tin "ate" complex from epoxystannane **15**. This was performed *via* tin NMR studies, by adding Bu^{n}Li (with and without diamine and polar co-solvent) to a frozen (in liquid N_2) solution of stannylated epoxide **15**. Following the reaction by ^{119}Sn NMR did not allow the observation of a potential signal (around −280 ppm) of an "ate" complex, such as **20** (Fig. 1), likely ruling out the possible existence of an equilibrium between such a complex and the lithiated epoxide.[27]



20

Fig. 1

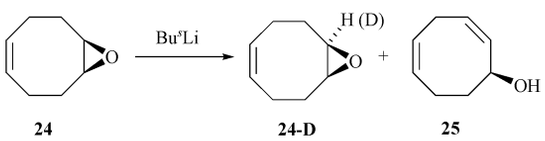
We next examined the scope of this new methodology with alternative *meso*-epoxides. 5,6-Disubstituted epoxide **21** has previously been successfully used in the enantioselective desymmetrisation transannular C–H insertion reaction (*cf.* formation of **3** in Scheme 2).[28,29] Epoxide **21** was fully deuterated under the same reaction conditions as cyclooctene oxide **1** using Bu^{s}Li (1.25 equiv.) and (−)-sparteine (1.3 equiv.), albeit after a slightly longer reaction time (2.5 h). An increased stability was observed for lithiated **21**, since an overnight reaction at −90 °C also produced complete D incorporation, with no by-product observed. The increase in both lithiation time and oxiranyl anion stability might be due to the slow equilibrium previously established between the two enantiomeric conformers of **21**.[28] The steric bulk of the backside of the ring might also account for the extent of stability of the lithiated epoxide derived from **21**. Having established the time required for complete deprotonation of epoxide **21** with TMEDA (12 h), we managed to trap the intermediate lithiated epoxide with benzaldehyde and *N*,*N*-dimethylbenzamide to give the alcohol **22** (1.5 : 1 mixture of diastereomers) and ketone **23** in 85% and 84% yields, respectively. In the presence of (−)-sparteine **2**, (+)-**22** and (−)-**23** were isolated in 79% and 84% yields with 77% and 74% ee, respectively (Scheme 6). The absolute



Scheme 6

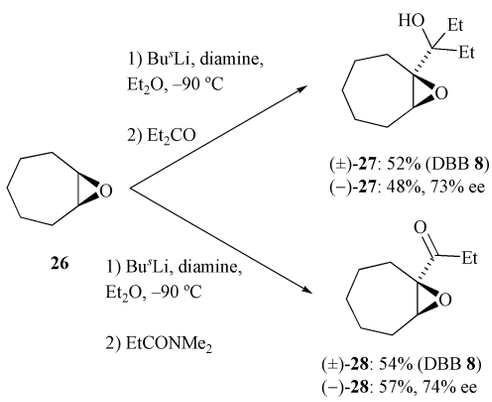
configuration of (−)-**23** is as shown in Scheme 6 and is assigned from the known sense of asymmetric induction in the deprotonation–rearrangement of the epoxide **21** using (−)-sparteine **2**.[28]

The last 8-membered cycloalkene epoxide examined was 1,2-epoxycyclooct-5-ene **24** (Scheme 7). Alexakis and co-workers have reacted epoxide **24** with Bu^{s}Li–(−)-sparteine in Et_2O at −90 °C for 6 h, followed by warming to room temperature; under these conditions they isolated the allylic alcohol **25** in 85% yield and 62% ee.[30] We hoped that under slightly different conditions the supposed intermediate lithiated epoxide could be trapped with deuterated methanol. However, from the reactions carried out in Et_2O, it appears that it is not possible at this time to trap the oxiranyl anion of epoxide **24** with deuterium, as rearrangement to the allylic alcohol **25** is too facile. Using Bu^{s}Li (1.3 equiv.) and (−)-sparteine **2** (1.3 equiv.) in Et_2O at −90 °C and quenching after 10 min gave a ratio 1 : 13, **24** : **25**; if quenched after 20 min this increased to 1 : 46. Changing from Et_2O to hexane did slow down the rearrangement, and after 3 h at −90 °C, 30% D incorporation was observed (but with a 1 : 1 ratio **24/24-D** : **25**). Changing the ligand from (−)-sparteine **2** to DBB **8** also reduced the rate of formation of **25**, but no D incorporation was observed in **24** (Scheme 7).



Scheme 7

This research has been extended to other cycloalkene epoxides. It proved possible to trap the oxiranyl anion derived from cycloheptene oxide **26** using DBB **8**, which required 16 h to obtain complete D incorporation (TMEDA did not give satisfactory results with epoxide **26**). Compared with cyclooctene oxide **1**, a significantly longer reaction time was required with **26**, when (−)-sparteine was used, to obtain complete D incorporation (12 h *vs*. 1 h) and also side products [cycloheptanone (18%) and alkene from reductive alkylation (8%)][4] were obtained. The lower reactivity toward α-deprotonation, when using (−)-sparteine, of cycloheptene oxide **26** compared with cyclooctene oxide **1** may be due to the reduced (angle) strain in **26** (angle strain has been calculated at 3.4 kJ mol^{-1} for **26** and 4.7 kJ mol^{-1} for **1**).[31] With DBB as the ligand, trapping with 3-pentanone and *N*,*N*-dimethylpropionamide allowed the isolation of the corresponding substituted epoxides **27** and **28**, albeit in moderate yields (52% and 54% respectively, Scheme 8). Using (−)-sparteine **2** instead of DBB **8** as the ligand gave similar yields of (−)-**27** and (−)-**28** (48% and 57%, respectively) and ees comparable to those obtained in the cyclooctene oxide **1** series (73% and 74% ee, respectively). The absolute configurations of (−)-**27** and (−)-**28** are tentatively assigned as shown in Scheme 8, in line with all our previous observations on enantio-



Scheme 8

selective α-deprotonation of epoxides using (−)-sparteine **2**, where proton removal at the *R*-epoxide stereocentre is consistently seen.[4]

Attempts to generate and trap the oxiranyl anions from cyclohexene and cyclopentene oxides were unsuccessful (the presumed intermediate oxiranyllithium species underwent typical carbenoid rearrangements and reductive alkylation).[4] Trapping an acyclic alkene epoxide, such as *cis*-5-decene oxide[32] with D_2O resulted in 90% D incorporation using Bu^{s}Li (2.5 equiv.)–(−)-sparteine **2** (2.5 equiv.) in Et_2O at −90 °C for 4 h. However, the isolated yield of recovered epoxide was low (below 40%), and a significant amount of volatile (*E*)-5-*sec*-butyldec-5-ene (arising from reductive alkylation)[33] was isolated (34%). This trend was confirmed by an *in situ* trapping experiment with TMSCl (3 equiv.) which only led to an 18% yield of the corresponding epoxysilane.[34]

As cycloheptene oxide **27** was successful under the desymmetrisation conditions, other 7-membered cycloalkene oxides were examined that possessed additional functionality (Fig. 2).

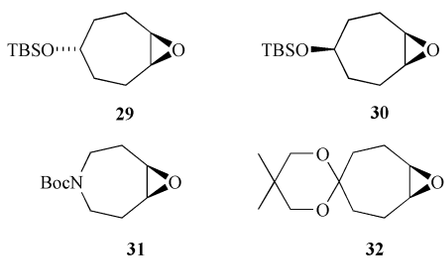
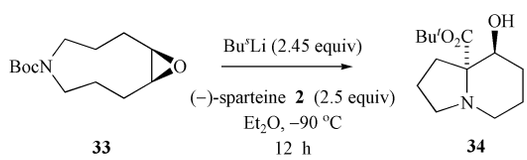


Fig. 2

Deuteration studies using CD_3OD were undertaken with epoxides **29** and **30**[35] and it was found that in Et_2O after 18 h at −90 °C the epoxides were inert to Bu^{s}Li (either 1.25 or 2.45 equiv.)–(−)-sparteine **2** (either 1.3 or 2.5 equiv.), since the epoxides were recovered with no deuterium incorporation. When the reaction was run at −78 °C, after 1 h 18% D incorporation was observed with epoxide **29**, however after 3 h no D incorporation was observed and multiple products had formed. Therefore epoxide **30** was not investigated at −78 °C. Epoxide **31** also proved inert at −90 °C after 18 h, irrespective of whether 1.3 or 2.5 equiv. of Bu^{s}Li–(−)-sparteine **2** was used. Unfortunately, increasing the reaction temperature to −78 °C for 18 h (either 1.3 or 2.5 equiv. of Bu^{s}Li–(−)-sparteine **2**) had a detrimental effect, as epoxide **31** was mainly decomposed to a number of unidentified products and as the small amount of epoxide remaining did not have any D incorporation. Lastly, epoxide **32** was examined. It had already been shown that the neopentyl glycol protecting group was stable under similar reaction conditions.[8b] However, as with epoxides **29**–**31** at −90 °C, no reaction occurred, and at −78 °C epoxide **32** was not stable. The investigation of epoxides **26** and **29**–**32** highlights the point that modest changes in substrate structure can have a significant affect on reactivity in the current chemistry. The presence of the additional functionality in epoxides **29**–**32** appears to reduce the ability for Bu^{s}Li–(−)-sparteine to effect their α-lithiation at a low enough temperature (−90 °C) for the intermediate oxiranyl anions to survive to undergo subsequent synthetically useful nucleophilic reactions.

Azacyclic epoxide **33**[28] (Scheme 9, for which the precursor alkene was prepared by a slightly improved method—see Experimental section) required Bu^{s}Li (2.5 equiv.)–(−)-sparteine



Scheme 9

2 (2.5 equiv.) to observe any reaction at −90 °C. The requirement for 2.5 equiv. of Bu^{s}Li–(−)-sparteine **2** in order to observe reactivity with azacyclic epoxide **33** may be due to complexation of 1 equiv. of the base–ligand with the *N*-Boc functionality. However, lithiation at −90 °C for 12 h only led to the rearranged ester **34** (45%), previously reported (Scheme 9).[28]

In summary, the present work illustrates a conceptually different approach to previous asymmetric desymmetrisation strategies of *meso*-epoxides: in the current work a chemical transformation occurs selectively at one of the enantiotopic epoxide termini, but the useful epoxide functional group is retained in the product, resulting in a new method for chiral epoxide synthesis. The results described herein demonstrate the process is currently viable in cyclooctene-derived epoxides, and for cycloheptene oxide. For the cyclooctene-derived epoxides, the ligand used in combination with the organolithium to effect deprotonation plays a key role in allowing the deprotonation to occur at low temperature. The ligand may also sterically 'shield' the lithiated epoxide intermediate from (currently) undesired decomposition pathways, such that the usual reaction pathway for these particular intermediates (transannular C–H insertion)[4] does not occur. Another important factor in the success of the current chemistry is that the deprotonation can be achieved with just over one equivalent of base. Compared with the cyclooctene epoxides, cycloheptene oxide is somewhat less susceptible to deprotonation, however in the presence of a diamine this can be achieved without significant further reaction of the intermediate lithiated epoxide. However, substituted cycloheptene oxides, cyclohexene and cyclopentene oxide, and a representative acyclic alkene oxide are currently not viable substrates for this chemistry. With these substrates, the ligands examined thus far are not capable of assisting α-lithiation to give controlled generation of oxiranyl anions.

While this paper reports the first steps toward a new approach for the elaboration of simple achiral epoxides to chiral epoxides, a significant challenge remains in expanding the scope of the chemistry so that it becomes viable with a wider range of substrates. Future progress in this area will likely require a greater understanding of the factors that affect epoxide deprotonation, along with those factors that contribute to the stability of the oxiranyl anion intermediate, yet still allow the latter to function effectively in electrophile trapping reactions.

Experimental

General directions

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl under argon; CH_2Cl_2 and benzene from CaH_2 under argon. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available aluminium-backed plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were dried over $MgSO_4$ unless stated otherwise. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Light petroleum refers to the fraction with bp 40–60 °C. $[a]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films unless stated otherwise. Peak intensities are specified as strong (s), medium (m) or weak (w). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise with a Bruker DPX 250, JEOL EX400 or Bruker AMX500 spectrometer. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C (central line of t) 77.0]. Coupling constants (*J*) are given in Hz. OH signals were assigned by the absence of cross-peaks in ^{1}H–^{13}C correlation spectra. Chiral stationary phase HPLC was performed using a Daicel Chiralcel OD column (4.6 mm × 250 mm) or Daicel Chiralpak AD column (4.6 mm × 250 mm) on a Gilson System with 712 Controller Software and a 118 UV–Vis detector set at 254 nm. Chiral GC was performed using a ThermoQuest CE Instruments TRACE GC, running ChromCard for TRACE software, fitted with a Chrompack-CP-Chiralsil-DEX-CB column at the stated temperature/temperature gradient. Retention times for major (t_R mj) and minor (t_R mn) enantiomers are given in minutes.

3,7-Dibutyl-3,7-diazabicyclo[3.3.1]nonane 8. To neat 3,7-Dibutyl-3,7-diaza-9-oxobicyclo[3.3.1]nonane **7**[20] (11.3 g, 44.7 mmol) was added hydrazine monohydrate (11.2 ml, 11.5 g, 223.5 mmol). The mixture was refluxed for 2 h, then cooled to room temperature, diluted with Et_2O (200 ml), washed with water (2 × 200 ml), brine (100 ml) and dried. To the resultant yellow oil was added powdered KOH (6.76 g, 49 mmol). The mixture was heated at 90 °C for 12 h and then distilled under reduced pressure (0.08 mbar, 115 °C) to yield 3,7-dibutyl-3,7-diazabicyclo[3.3.1]nonane **8** (5.2 g, 49%) as a colourless oil whose spectral data were consistent with those reported earlier.[20]

Once allowed to cool to 0 °C, the distillation residue was carefully diluted with conc. HCl (50 ml). The mixture was refluxed for 12 h, cooled to room temperature, diluted with water and extracted with Et_2O. The aqueous layer was basified to pH 11 with KOH and then extracted with Et_2O (3 × 100 ml). The combined organic layers were washed with brine, dried and evaporated under reduced pressure giving recovered 3,7-dibutyl-3,7-diaza-9-oxobicyclo[3.3.1]nonane **7** (3.3 g).

Typical procedure for lithiation–electrophile trapping of cyclooctene oxide 1 in the presence of a diamine

The diamine (2.6 mmol) was added dropwise to a solution of RLi (1.4 M, 2.5 mmol) in Et_2O (8 ml) at −90 °C. This mixture was stirred for 1 h at −90 °C. A solution of cyclooctene oxide **1** (2.0 mmol) in Et_2O (2 ml), pre-cooled to −90 °C, was then added rapidly by cannula to the solution of ligand–RLi and the reaction mixture was then stirred at −90 °C for 3 h. Neat electrophile (3.0 mmol) was then added dropwise, and the reaction was then allowed to warm to room temperature over 5 h. After this time H_3PO_4 (0.5 M, 25 ml) was added, the organic phase was washed with $NaHCO_3$ (25 ml) and brine (25 ml). The aqueous layers were extracted twice with Et_2O (25 ml) and the combined organic phases were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, Et_2O in petrol) gave the substituted epoxide.

(9-Oxabicyclo[6.1.0]non-1-yl)phenylmethanol 9. R_f (pentane–ether: 9 : 1) 0.05; $[a]_D^{24}$ +20.1 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3428s, 2927s, 2858m, 1469m, 1453m, 1066m, 1043m, 1022m, 929m, 701m; δ_H (200 MHz) 7.41–7.26 (10 H, m), 4.78 (1 H, d, *J* 2.1), 4.70 (1 H, d, *J* 8.2), 3.34 (1 H, dd, *J* 10.1, 4.6), 2.98 (1 H, s), 2.70–2.63 (2 H, m), 2.33–2.23 (2 H, m), 2.08–2.02 (2 H, m), 1.69–1.20 (20 H, m); δ_C (50 MHz) 141.3, 139.8, 128.7, 128.2, 128.1, 128.0, 127.4, 127.3, 75.3, 72.1, 64.5, 64.1, 60.2, 57.8, 28.5, 27.8, 26.8, 26.7, 26.1, 26.0, 25.8, 25.2, 24.6; *m*/*z* [CI + (NH_3)] 250.1804 (M + NH_4^+. $C_{15}H_{24}NO_2$ requires 250.1807), 233 (100%), 215 (45), 199 (32). The ee was determined to be 76% after MnO_2 oxidation [MnO_2 (16 equiv.), CH_2Cl_2, 25 °C, 12 h] to ketone **10**; chiral GC as for **10** below.

(9-Oxabicyclo[6.1.0]non-1-yl)phenylmethanone 10. R_f (pentane–ether: 9 : 1) 0.7; $[a]_D^{24}$ −91.5 (c = 1.0 in $CHCl_3$) (from reaction with Bu^{s}Li); ν_{max}/cm^{-1} 2929m, 1679s, 1468m, 1448m, 1209s, 1177s, 710m; δ_H (200 MHz) 8.11–8.05 (2 H, m), 7.61–7.41 (3 H, m), 3.12 (1 H, dd, *J* 10.0, 4.0), 2.49–2.41 (1 H, m), 2.29–2.21 (1 H, m), 1.83–1.53 (10 H, m); δ_C (50 MHz) 197.8, 134.3, 133.3, 129.4, 128.4, 65.5, 59.8, 29.1, 26.7, 26.0, 25.8, 25.5, 25.0; *m*/*z* [CI

+ (NH_3)] 248.1653 (M + NH_4^+. $C_{15}H_{22}NO_2$ requires 248.1651), 230 (25%), 214 (30), 105 (70), 77 (100). The ee was determined to be 77% by chiral GC (130 °C, 0.7 ml min^{-1}): $t_R$mn 83.7, $t_R$mj 85.6.

1-(9-Oxabicyclo[6.1.0]non-1-yl)propan-1-ol 11. R_f (pentane–ether: 9 : 1) 0.1; $[a]_D^{24}$ −25.3 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3430m, 2920s, 2860m, 1465w, 1106m, 976m, 926m, 836m; δ_H (400 MHz) 3.66 (1 H, dd, J 8.8, 2.9), 3.51 (1 H, dd, J 9.5, 3.8), 3.14 (1 H, dd, J 9.8, 4.8), 2.94 (1 H, dd, J 9.7, 4.6), 2.26–2.03 (6 H, m), 1.77–1.29 (24 H, m), 1.00 (6 H, t, J 7.4); δ_C (50 MHz) 74.4, 70.0, 64.0, 63.7, 60.5, 58.0, 28.3, 27.7, 27.0, 26.8, 26.4, 26.3, 26.2, 26.1, 26.0, 25.8, 25.4, 25.3, 24.9, 10.7, 9.8; m/z [CI + (NH_3)] 202.1805 (M + NH_4^+. $C_{11}H_{24}NO_2$ requires 202.1807), 185 (20%), 167 (100), 151 (90). The ee was determined to be 76% after Dess–Martin oxidation [periodane (1.1 equiv.), CH_2Cl_2, 25 °C, 20 min] to ketone **13**; chiral GC as for **13** below.

3-(9-Oxabicyclo[6.1.0]non-1-yl)pentan-3-ol 12. R_f (pentane–ether: 9 : 1) 0.2; $[a]_D^{24}$ −41.6 (c = 1.0 in $CHCl_3$) (from reaction with Bu^{s}Li); ν_{max}/cm^{-1} 3515s, 2968s, 2936m, 1461m, 1369w, 1301m, 1151m, 1038s, 961m, 920m; δ_H (400 MHz) 2.97–2.93 (1 H, m), 2.55 (1 H, s), 2.13–2.03 (2 H, m), 1.65–1.31 (14 H, m), 0.89 (3 H, t, J 7.4), 0.82 (3 H, t, J 7.4); δ_C (50 MHz) 73.4, 65.5, 56.2, 31.4, 28.8, 27.9, 27.6, 26.4, 26.3, 26.2, 24.7, 8.0, 7.3; m/z [CI + (NH_3)] 230.2123 (M + NH_4^+. $C_{15}H_{28}NO_2$ requires 230.2120), 213 (57%), 195 (100), 179 (90). The ee was determined to be 77% by chiral GC (130 °C, 0.5 ml min^{-1}): $t_R$mn 28.8, $t_R$mj 30.7.

1-(9-Oxabicyclo[6.1.0]non-1-yl)propan-1-one 13. R_f (pentane–ether: 9 : 1) 0.6; $[a]_D^{24}$ +27.5 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2974s, 2919m, 2856m, 1708s, 1464m, 1448w, 1404m, 1117m, 1027s, 924m; δ_H (200 MHz) 3.03 (1 H, dd, J 9.5, 3.8), 2.51–2.20 (4 H, m), 1.61–1.24 (10 H, m), 0.94 (3 H, t, J 7.3); δ_C (50 MHz) 210.8, 64.1, 60.4, 30.2, 28.9, 27.9, 26.6, 26.4, 26.1, 24.6, 7.4; m/z [CI + (NH_3)] 200.1653 (M + NH_4^+. $C_{11}H_{22}NO_2$ requires 200.1651), 183 (7%), 167 (100), 137 (20). The ee was determined to be 78% by chiral GC (130 °C, 0.7 ml min^{-1}): $t_R$mn 8.2, $t_R$mj 9.4.

Ethyl 9-oxabicyclo[6.1.0]nonane-1-carboxylate 14. R_f (pentane–ether: 9 : 1) 0.7; $[a]_D^{24}$ −35.4 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2919s, 2859m, 1733s, 1467m, 1448w, 1306m, 1201m, 1156m, 1051s, 935m, 849m; δ_H (200 MHz) 4.18 (2 H, q, J 7.2), 3.28 (1 H, dd, J 10.0, 4.1), 2.50–2.41 (1 H, m), 2.24–2.14 (1 H, m), 1.79–1.29 (10 H, m), 1.26 (3 H, t, J 7.2); δ_C (50 MHz) 170.8, 60.9, 60.0, 59.2, 27.5, 26.7, 26.6, 26.5, 26.0, 24.7, 14.0; m/z [CI + (NH_3)] 216.1600 (M + NH_4^+. $C_{11}H_{22}NO_3$ requires 216.1600), 199 (60%), 183 (70), 125 (20). The ee was determined to be 81% by chiral GC (110 °C, 0.7 ml min^{-1}): $t_R$mn 28.3, $t_R$mj 29.8.

Tributyl(9-oxabicyclo[6.1.0]non-1-yl)stannane 15. R_f (pentane–ether: 9 : 1) 0.8; $[a]_D^{24}$ −38.2 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2958s, 2919s, 2848m, 1472m, 1456m, 1413m, 1373w, 1070s, 1019m, 921m; δ_H (500 MHz) 2.81 (1 H, dd, J 10, 4.5), 2.18–2.15 (2 H, m), 1.63–1.33 (23 H, m), 0.96–0.91 (14 H, m); δ_C (50 MHz) 62.5, 59.4, 32.3, 29.1, 27.4, 26.9, 26.7, 26.6, 26.2, 25.8, 13.6, 8.8; δ_{Sn} (186.4 MHz) −26.0; m/z [CI + (NH_3)] 416.2098 (M^+. $C_{20}H_{40}OSn$ requires 416.2101), 420 (20%), 418 (15), 417 (20), 416 (100), 415 (40), 414 (75), 413 (30), 412 (45). The ee was determined to be 79% after reaction with BuLi and trapping with 3-pentanone to give alcohol **12** [Bu^{n}Li (1.3 equiv.), TMEDA (2 equiv.), 3-pentanone (1.6 equiv.), THF, −90 °C, 10 min]; chiral GC as for **12** above.

Trimethyl(9-oxabicyclo[6.1.0]non-1-yl)stannane 16. R_f (pentane–ether: 9 : 1) 0.8; $[a]_D^{24}$ −34.5 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2925s, 2859s, 1474m, 1449m, 1184m, 1021s, 922m; δ_H (200 MHz) 2.83–2.76 (1 H, m), 2.20–2.12 (2 H, m), 1.60–1.38 (10 H, m), 0.15 (9 H, s); δ_C (50 MHz) 58.2, 47.6, 30.9, 30.4, 27.0, 26.9, 24.9, 22.6, −10.9; δ_{Sn} (186.4 MHz) −2.6; m/z [CI + (NH_3)] 290.0689 (M^+. $C_{11}H_{22}OSn$ requires 290.0693), 294 (20%), 292 (15), 290 (100), 289 (35), 288 (75), 286 (45), 287 (30), 291 (10). The ee was determined to be 78% after reaction with BuLi and trapping with 3-pentanone to give alcohol **12** [Bu^{n}Li (1.3 equiv.), TMEDA (2 equiv.), 3-pentanone (1.6 equiv.), THF, −90 °C, 10 min]; chiral GC as for **12** above.

Trimethyl(9-oxabicyclo[6.1.0]non-1-yl)silane 17. R_f (pentane–ether: 9 : 1) 0.8; $[a]_D^{24}$ −33.1 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2928s, 1471m, 1448m, 1247m, 1019s; δ_H (200 MHz) 2.81–2.56 (1 H, m), 2.18–2.05 (2 H, m), 1.63–1.25 (10 H, m), 0.08 (9 H, s); δ_C (50 MHz) 58.9, 55.7, 29.1, 26.8, 26.5, 26.4, 26.3, 25.2, −3.3; m/z [CI + (NH_3)] 199.1517 (M + H^+. $C_{11}H_{22}OSi$ requires 199.1518), 183 (10%), 169 (7), 155 (10), 143 (17), 109 (40), 90 (100). The ee was determined to be 74% by chiral GC (80 °C, 0.5 ml min^{-1}) $t_R$mn 97.4, $t_R$mj 101.4.

[4,5-Bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]-nonan-1-yl]phenylmethanol 22. R_f (pentane–ether: 8 : 2) 0.4; $[a]_D^{24}$ +3.0 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3515m, 2960s, 2929m, 2896m, 2847m, 1465m, 1252m, 1179m, 1030w, 890m, 710m; δ_H (C_7D_8, 250 MHz, 90 °C) 7.38–7.30 (2 H, m), 7.25–7.11 (3 H, m), 4.42–4.39 (1 H, br s), 4.05–3.90 (2 H, m), 2.66 (1 H, t, J 7.0), 1.99–1.40 (8 H, m), 0.97 (18 H, s), 0.14 (3 H, s), 0.08 (3 H, s), 0.07 (6 H, s); δ_C (C_7D_8, 62.5 MHz, 90 °C) 141.5, 128.3, 127.8, 127.3, 78.4, 78.1, 76.2, 63.6, 60.3, 58.7, 31.5, 30.7, 26.0, 24.0, 23.7, 18.3, 18.2, −4.5, −4.7, −4.8; m/z [CI + (NH_3)] 493.3174 (M + H^+. $C_{27}H_{49}O_4Si_2$ requires 493.3169), 515 (100%), 493 (65), 454 (55), 413 (50), 391 (31), 361 (30), 342 (60), 229 (65). The ee was determined to be 77% after MnO_2 oxidation [MnO_2 (16 equiv.), CH_2Cl_2, 25 °C, 12 h] to ketone **23**; chiral HPLC as for **23** below.

[4,5-Bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]-nonan-1-yl]phenylmethanone 23. R_f (pentane–ether: 96 : 4) 0.5; $[a]_D^{24}$ −31.2 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2955s, 2924m, 2889m, 2853m, 1680s, 1468m, 1247m, 1174m, 1025w, 894m, 704m; δ_H (C_7D_8, 250 MHz, 90 °C) 8.12 (2 H, br d, J 7.5), 7.20 (1 H, br d, J 6.8), 7.17 (2 H, br d, J 7.5), 4.35–4.19 (2 H, m), 2.92 (1 H, dd, J 9.0, 4.3), 2.18–1.51 (8 H, m), 0.99 (9 H, s), 0.97 (9 H, s), 0.18 (6 H, s), 0.13 (6 H, s); δ_C (C_7D_8, 62.5 MHz, 90 °C) 197.5, 135.1, 133.0, 129.8, 128.4, 77.4, 76.4, 65.4, 59.3, 31.0, 30.8, 26.1, 25.2, 23.3, 18.3, 18.2, −4.5, −4.6, −4.8, −4.9; m/z [CI + (NH_3)] 491.3020 (M + H^+. $C_{27}H_{47}O_4Si_2$ requires 491.3013), 475 (40%), (12%), 105 (100%), 90 (95%). The ee was determined to be 74% by chiral HPLC (OD column, 100% heptane, 0.8 cm^3 min^{-1}): $t_R$mn 15.8, $t_R$mj 30.5.

3-(8-Oxabicyclo[5.1.0]oct-1-yl)pentan-3-ol 27. R_f (pentane–ether: 8 : 2) 0.4; $[a]_D^{24}$ −18.9 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3475m, 2924s, 2860m, 1459w, 1165w, 957w, 916w; δ_H (250 MHz) 3.34 (1 H, dd, J 6.7, 1.9), 2.14–1.42 (14 H, m), 0.92 (3 H, t, J 7.5), 0.91 (3 H, t, J 7.5); δ_C (62.5 MHz, $CDCl_3$) 74.6, 66.3, 56.6, 31.5, 31.3, 29.9, 28.3, 27.9, 24.4, 23.7, 8.3, 8.1; m/z [CI + (NH_3)] 199.1701 (M + H^+. $C_{12}H_{23}O_2$ requires 199.1698), 216 (40%), 199 (40), 198 (40), 181 (98), 165 (100). The ee was determined to be 73% by chiral GC (130 °C, 0.5 ml min^{-1}): $t_R$mn 20.5, $t_R$mj 23.1.

1-(8-Oxabicyclo[5.1.0]oct-1-yl)propan-1-one 28. R_f (pentane–ether: 96 : 4) 0.45; $[a]_D^{24}$ −10.5 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2975s, 2927m, 2846m, 1705s, 1454m, 1366w, 1199m, 1090m; δ_H (250 MHz) 3.19 (1 H, dd, J 6.0, 3.7), 2.55–2.25 (3 H, m), 2.06–1.44 (9 H, m), 1.02 (3 H, t, J 7.4); δ_C (62.5 MHz) 212.6, 66.6, 60.6, 31.5, 29.7, 29.1, 28.8, 25.3, 24.4, 7.9; m/z [CI + (NH_3)] 169.1232 (M + H^+. $C_{10}H_{17}O_2$ requires 169.1229), 186 (100%), 169 (70). The ee was determined to be 74% by chiral GC (110 °C, 0.5 ml min^{-1}): $t_R$mn 12.4, $t_R$mj 14.7.

Typical procedure for the synthesis of α-alkylcyclooctene oxide

To a solution of tributyl(9-oxabicyclo[6.1.0]non-1-yl)stannane **15** (0.5 mmol) and TMEDA (2 equiv., 1.0 mmol) in THF (2.5 ml) at −90 °C was added Bu^{n}Li (1.3 equiv., 0.65 mmol). The alkyl iodide (3 equiv., 1.5 mmol) was then added in one portion after 0.5 min and the reaction mixture was stirred at this temperature for 10 min. After quenching with H_3PO_4 (0.5 M, 15 ml), and extraction with Et_2O (3 × 10 ml), the combined organic phases were washed with brine (15 ml), dried and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 5% Et_2O in petrol) gave the alkylated epoxide.

α-Methylcyclooctene oxide 18. R_f (pentane–ether: 9 : 1) 0.50; ν_{max}/cm^{-1} 2930s, 1724w, 1263w, 1216w; δ_H (400 MHz) 2.66 (1 H, dd, *J* 10.3, 4.4), 2.17–2.10 (1 H, m), 1.91–1.85 (1 H, m), 1.66–1.32 (10 H, m), 1.30 (3 H, s); δ_C (50 MHz) 63.2, 59.79, 31.28, 27.87, 26.67, 26.05, 25.31, 21.58; *m*/*z* [CI + (NH_3)] 141.1276 (M + H$^+$. $C_9H_{17}O$ requires 141.1279), 158 (100%), 141 (83), 140 (65).

α-Butylcyclooctene oxide 19. R_f (pentane–ether: 95 : 5) 0.61; ν_{max}/cm^{-1} 2929s, 2859w, 1468w, 1260w, 1023w, 804w; δ_H (400 MHz) 2.69 (1 H, dd, *J* 9.9, 4.5), 2.03 (1 H, dt, *J* 13.8, 3.4), 2.19–2.11 (1 H, m), 1.94–1.85 (1 H, m), 1.71–1.17 (15 H, m), 0.91 (3 H, t, *J* 7.0); δ_C (50 MHz) 65.8, 62.2, 33.7, 28.2, 27.9, 26.7, 26.3, 26.2, 25.8, 25.4, 23.0, 14.1; *m*/*z* [CI + (NH_3)] 200.2014 (M + NH_4^+. $C_{12}H_{26}NO$ requires 200.2021), 183 (53%), 165 (100).

***tert*-Butyl 8-oxa-4-azabicyclo[5.1.0]octane-4-carboxylate 31.** Peracetic acid (1 ml, 36% w/w in dilute AcOH; 4.8 mmol) was added to a stirred mixture of *tert*-butyl 2,3,6,7-tetrahydroazepine-1-carboxylate[36] (602 mg, 3 mmol), Na_2CO_3 (1.3 g, 12 mmol) and NaOAc (13 mg, 0.14 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The reaction was warmed to 25 °C and stirred for a further 15 h. Et_2O (30 ml) was added and the organic layers were washed with water (30 ml), saturated aq. $NaHCO_3$ (2 × 20 ml), brine (20 ml), dried and evaporated under reduced pressure to give epoxide **31** (520 mg, 81%) as a colourless oil; R_f (light petroleum–ether: 7 : 3) 0.18; ν_{max}/cm^{-1} 2975s, 1694s, 1417s, 1336s, 1172s, 944s; δ_H (400 MHz) 3.17 (2 H, br s, epoxide), 2.56–2.89 and 3.5–3.86 (4 H, 2 × m, 2 × CH_2N), 1.92–2.21 (4 H, m, 2 × CH_2), 1.41 (9 H, s, 3 × CH_3); δ_C (100 MHz) 56.0, 55.8, 53.4, 43.4, 43.1, 28.9, 28.4, 28.1; *m*/*z* [CI + (NH_3)] 214.1438 (M + H$^+$. $C_{11}H_{20}NO_3$ requires 214.1443), 175 (40%), 158 (40), 114 (100).

3,3-Dimethyl-1,5-dioxaspiro[5.6]dodec-9-ene oxide 32. Neopentyl glycol (832 mg, 8 mmol) was added to a stirred mixture of 4-cyclohepten-1-one[37] (770 mg, 7 mmol) and PTSA (27 mg, 0.14 mmol) in benzene (50 ml). The reaction was refluxed using a Dean–Stark trap for 24 h. Light Petroleum (30 ml) was added and the organic layer was washed with saturated aq. $NaHCO_3$ (2 × 20 ml), brine (20 ml), dried and evaporated under reduced pressure to give 3,3-dimethyl-1,5-dioxaspiro[5.6]dodec-9-ene (775 mg, 57%) as a colourless oil, which was used in the next step without further purification; R_f (light petroleum–ether: 5 : 2) 0.75; ν_{max}/cm^{-1} 2953s, 2866s, 1110s, 912s, 733s; δ_H (400 MHz) 5.48–5.55 (2 H, m, 2 × CH=), 3.46 (4 H, s, 2 × CH_2O), 2.02–2.09 (4 H, m, 2 × CH_2), 1.85–1.93 (4 H, m, 2 × CH_2), 0.92 (6 H, s, 2 × CH_3); δ_C (100 MHz) 132.3, 131.9, 106.9, 70.3, 34.1, 28.4, 23.4, 23.0; *m*/*z* [CI + (NH_3)] 197.1539 (M + H$^+$. $C_{12}H_{21}O_2$ requires 197.1542), 128 (50%). Peracetic acid (1.4 ml, 36% w/w in dilute AcOH; 6.4 mmol) was added to a stirred mixture of 3,3-dimethyl-1,5-dioxaspiro[5.6]dodec-9-ene (775 mg, 4 mmol), Na_2CO_3 (1.7 g, 16 mmol) and NaOAc (18 mg, 0.19 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The reaction was warmed to 25 °C and stirred for a further 15 h. Et_2O (30 ml) was added and the organic layers were washed with water (30 ml), saturated aq. $NaHCO_3$ (2 × 20 ml), brine (20 ml), dried and evaporated under reduced pressure to give a colourless oil that solidified on standing. The product was purified by repeated trituration with cold light petroleum to give the epoxide **32** (399 mg, 63%) as a colourless solid (mp close to rt); R_f (petroleum ether–ether: 7 : 3) 0.21; ν_{max}/cm^{-1} 3430s (hydroscopic), 2959s, 2857s, 1107m, 916m; δ_H (400 MHz) 3.44 (2 H, s, CH_2O), 3.40 (2 H, s, CH_2O), 2.98–3.04 (2 H, m, 2 × CH epoxide), 1.67–2.00 (8 H, m, 4 × CH_2), 0.88 (6 H, s, 2 × CH_3); δ_C (100 MHz) 99.4, 70.0, 69.9, 55.1, 30.0, 29.6, 22.6, 21.5; *m*/*z* [CI + (NH_3)] 213.1489 (M + H$^+$. $C_{12}H_{21}O_3$ requires 213.1491), 142 (40%), 128 (30).

(*Z*)-*N*-(4-Methylbenzylsulfonyl)-2,3,4,7,8,9-hexahydroazonine. A 3 l three-necked round-bottomed-flask was equipped with a reflux condenser and one dropping funnel. The flask was charged with toluene (600 ml), Bu_4NI (1.14 g, 3.1 mmol), NaOH (18.6 g, 0.46 mol) and water (44 ml). The funnel was charged with a solution of (*Z*)-1,8-bis(4-methylbenzylsulfonyloxy)oct-4-ene (1 g, 2.21 mmol) in toluene (125 ml). The funnel was allowed to discharge the ditosylate dropwise into the reaction flask over a period of 4 h and a solution of $TsNH_2$ (644 mg, 3.76 mmol) in hot toluene (125 ml, 70 °C) was added to the reaction flask by cannula at the same rate. A gentle reflux was maintained over 12 h and a second addition of (*Z*)-1,8-bis-(4-methylbenzylsulfonyloxy)oct-4-ene and $TsNH_2$ was similarly performed. After 10 h of gentle reflux, a third addition was performed and a fourth after 12 h. After 24 h at reflux, the solution was allowed to cool to room temperature. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 125 ml). The combined organic layers were washed with brine (125 ml), dried and evaporated under reduced pressure. Purification of the residue by column chromatography (from 0 to 30% Et_2O in petrol) gave a crystalline solid (1.8 g, 72%) for which spectral and physical data were identical with those reported earlier.[28]

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