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Organolithium-induced enantioselective alkylative double ring-opening of epoxides: synthesis of enantioenriched unsaturated amino alcohols☆

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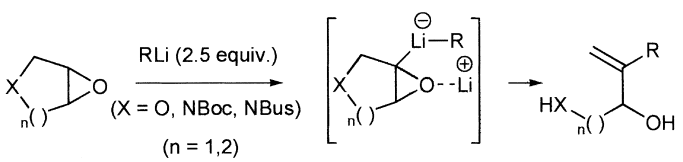
Abstract—The use of (−)-sparteine as an external chiral ligand in enantioselective organolithium-induced alkylative double ring-opening of dihydropyrrole epoxides and 7-azanorbornene-type epoxides gives unsaturated acyclic amino alcohols, and amino cyclohexenols in up to 87% ee.

1. Introduction

Enantioselective desymmetrisation of achiral materials is an attractive and powerful concept in asymmetric synthesis.[1] *meso*-Epoxides represent an important class of substrates for new desymmetrisation methodologies,[1,2] and base-induced enantioselective transformations of such epoxides by β-elimination[3] or α-deprotonation[4] are a focus of current interest. We recently reported the organolithium-induced alkylative deoxygenation of epoxides of dihydrofuran (Scheme 1, n=1, X=O) and dihydropyran (n=2, X=O),[5] as well as epoxides of dihydropyrrole [n=1, X=NBus (Bus=Bu^{t}SO$_2$)] and tetrahydropyridine (n=2, X=NBus)[6] to generate acyclic unsaturated diols and amino alcohols, respectively. These processes most likely proceed via α-deprotonation and insertion (possibly by a 1,2-metallate shift)[7] of a second equivalent of organolithium into the initially formed lithiated epoxide, followed by elimination.

Due to the widespread occurrence of the 1,2-amino alcohol motif in bioactive natural products, many pharmaceutical agents and in useful synthetic intermediates, auxiliaries, and ligands in catalysis, considerable importance is attached to new methods to access this moiety.[8] In conjunction with our studies into chiral ligand-assisted organolithium-induced enantioselective α-deprotonations of cycloalkene- and heterocycloalkene-derived epoxides,[4] we sought to develop the above alkylative desymmetrisation reaction of epoxides into an enantioselective entry to acyclic unsaturated 1,2-amino alcohols, as well as cyclic (2-aminocyclohex-5-en-1-ol) systems, and detail our results in these areas in the current paper.[9]



Scheme 1.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.02.055

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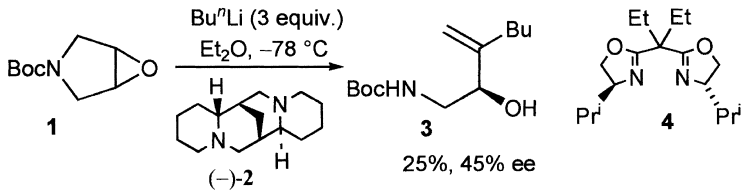
2. Results and discussion

Our initial investigations focused on the alkylative desymmetrisation of the simplest available achiral epoxides derived from dihydropyrrole (Scheme 2). The product distribution arising from the alkylative double ring-opening of such 3,4-epoxytetrahydropyrroles was previously found to be dependent on the nitrogen protecting group.[6] In the current study, the use of the Bus protecting group[10] was again found to result in superior yields of amino alcohol (in comparison to using Boc protection) in the ligand-assisted process. Thus, reaction of NBoc epoxide **1** under typical enantioselective desymmetrisation conditions [addition of epoxide to Bu^{n}Li and (−)-sparteine **2** (3 equiv. each) in Et_2O at −78 °C, followed after 1 h at −78 °C by warming to 0 °C (1 h)] gave amino alcohol (+)-**3** in only 25% yield, and 45% ee; the corresponding non-ligand mediated reaction with Bu^{n}Li in Et_2O had previously given **3** in 46% yield.[6] Switching to valine-derived bisoxazoline **4** as ligand with NBoc epoxide **1** returned mainly starting epoxide (90%), along with traces of NBoc pyrrole (7%). The sense of asymmetric induction observed in amino alcohol (+)-**3** using Bu^{n}Li/**2** with epoxide **1** is tentatively assigned as shown in Scheme 2. This assignment is by analogy with all our previous observations on organolithium-induced enantioselective α-deprotonation of epoxides[4] [medium-sized (8, 9 and 10-membered) cycloalkene epoxides,[11] silyloxysubstituted cyclooctene epoxides,[12] norbornene epoxide,[11] (*N*-Boc)-7-azanorbornene epoxide[13] and 3,4-epoxytetrahydrofuran[14]] using sparteine **2**, where proton removal at the *R*-epoxide stereocentre is consistently seen. Products from similar α-deprotonation–alkylation of related epoxides discussed later in this paper are similarly assigned by analogy as being derived from proton removal at the *R*-epoxide stereocentre when using sparteine **2**.

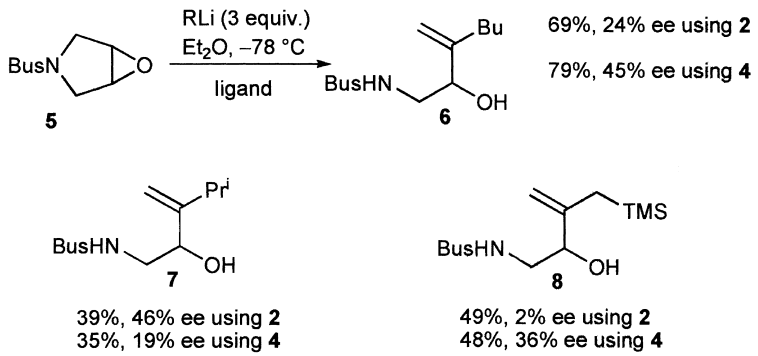
Using NBus epoxide **5** under the typical desymmetrisation conditions with (−)-sparteine **2** gave amino alcohol (+)-**6** in 69% yield, but in only 24% ee (Scheme 3); NBus pyrrole [confirmed by independent synthesis (88%) from Bu^tSO_2-NH_2[15] and 2,5-dimethoxytetrahydrofuran using P_2O_5[16]] was observed as a minor byproduct (18%).

Some variations to the standard reaction conditions with sparteine **2** were examined in an attempt to improve yields and/or asymmetric induction with NBus epoxide **5**. However, reducing the quantity of sparteine to one equivalent,[14] or initiating the reaction at −100 °C, or maintaining the reaction for a longer period (5 h) at −78 °C, or slowly warming up from a longer period (5 h) at −78 °C had little effect (52–64% yields, 16–27% ees). Several alternative ligands to sparteine were also investigated (Fig. 1).[17] No reaction was observed using diamine ligand **9**,[18] or using the amino alkoxide of **10**[19] (4 equiv. of Bu^{n}Li were used in this latter case), whereas with diether **11**[20] the desired amino alcohol (+)-**6** was observed (65% yield), but in only 6% ee. More encouraging was the use of bisoxazoline **4**, which gave (−)-**6** in 79% yield and 45% ee; 11% of NBus pyrrole was also isolated. The corresponding alanine- and *tert*-leucine-derived bisoxazolines were also studied, however these led to no improvement (33% yield, 43% ee, and 53% yield, 14% ee, respectively) compared with the use of bisoxazoline **4**. Maintaining the valine-derived bisoxazoline unit, but varying the linking *gem*-dialkyl group from diethyl to diisobutyl was also detrimental to yield (52%) and asymmetric induction (29% ee).

With NBus epoxide **5** two other organolithiums (Pr^{i}Li and $TMSCH_2Li$) were also investigated using sparteine **2** and bisoxazoline **4** as ligands (Scheme 3), so as to provide a comparison with the reactions of Bu^{n}Li. As observed in previous reactions with sparteine,[4] Pr^{i}Li provided higher asymmetric induction compared with Bu^{n}Li: isopropyl-substituted amino alcohol (+)-**7** was formed in 46% ee, compared with butyl-substituted (+)-**6** in 24% ee. In contrast, the secondary organolithium was less effective when using bisoxazoline **4** as ligand [(−)-**7**, 19% ee; (−)-**6**,



Scheme 2.



Scheme 3.

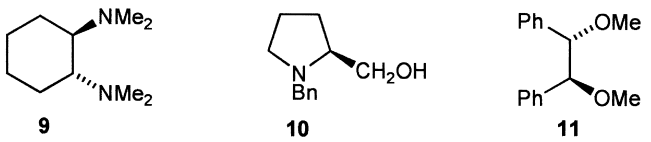


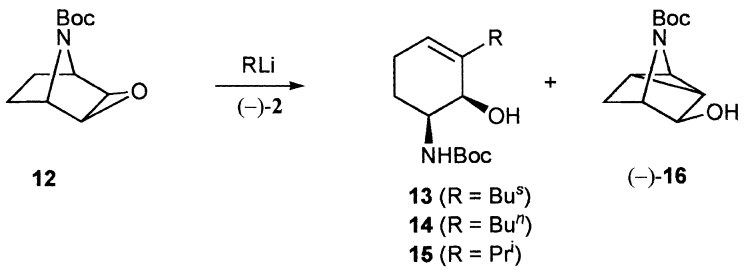
Figure 1. Ligands **9**–**11**.

45% ee]. Allylsilane **8** was formed essentially as the racemate when using sparteine **2**, and in 36% ee using bisoxazoline **4**.

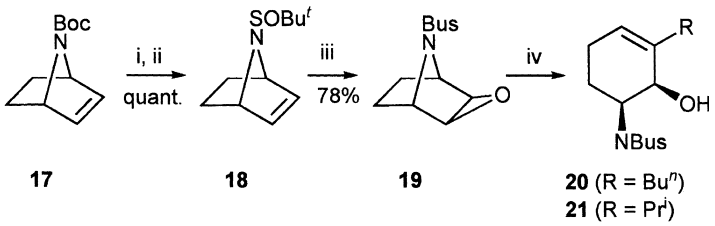
In seeking to extend the enantioselective alkylative desymmetrisation process to generate amino cyclohexenols we focused on NBoc azanorbornene epoxide **12** (Scheme 4). Previously, we had established that rearrangement of epoxide **12** by enantioselective deprotonation transannular C–H insertion was possible using substituted *aryl*lithiums in combination with (−)-sparteine **2**, or bisoxazoline ligands such as **4**, to give azanortricyclanol **16** in up to 60% yield and 87% ee; amino cyclohexenols (cf, **13**–**15**, but R=aryl) were not observed in these reactions.[13] Reaction of epoxide **12** with Bu^{s}Li in the presence of bisoxazoline **4** in Et_2O was also known to only give azanortricyclanol **16** [37%, 51% based on recovered starting material (brsm), 63% ee].[13] However, with epoxide **12**, the use of Bu^{s}Li in combination with sparteine **2** (3 equiv. each) in Et_2O at −78 °C for 5 h followed by warming to room temperature gave amino alcohol **13** as the major product (56%), along with a lesser quantity of the azanortricyclanol **16** (20%, 59% ee) and some recovered epoxide **12** (16%). The amino alcohol **13** obtained in this reaction was optically active, but the presence of diastereomers (due to the stereocentre in the Bu^s substituent) made the enantiomeric excess determination problematic. Nevertheless, this result suggested that reactions of alkyllithiums with azanorbornene oxide **12** could be an interesting avenue for further investigations.

Initial screenings with NBoc azanorbornene epoxide **12**[21] using Bu^{n}Li (3 equiv.) in the absence of an added ligand in THF, Et_2O or toluene at −78 °C established that Et_2O was the preferred solvent to preferentially generate the amino cyclohexenol **14** [42% isolated yield, 26% of **16**[21] also isolated; **14**:**16**, 1:0.5 (THF), 1:0.6 (Et_2O), 1:1 (toluene)]. Pleasingly, with Bu^{n}Li in the presence of sparteine **2** (3 equiv. each) in Et_2O the proportion of amino cyclohexenol **14** increased (**14**:**16**, 1:0.25) and (−)-**14** was isolated in 55% yield and 67% ee; the azanortricyclanol (−)-**16** was also isolated in 14% yield and 35% ee. The determination of absolute configuration of azanortricyclanol (−)-**16** has previously been communicated,[13] and the absolute configuration of (−)-**16** is as shown in Scheme 4. With Pr^{i}Li the amino cyclohexenol (−)-**15** was obtained in 51% yield and 87% ee [(−)-**16** was also isolated: 24%, 46% ee), demonstrating once again the higher enantiodiscrimination possible using this secondary organolithium with sparteine. Using slightly more Pr^{i}Li (3.5 equiv.) led to a significant improvement in isolated yield of the amino cyclohexenol (−)-**15** (78%, 87% ee), and in this case no azanortricyclanol **16** was detected; using 3.5 equiv. of Bu^{s}Li with epoxide **12** also led to a higher yield of amino alcohol **13** (74%, cf. 56% with 3 equiv.) along with some azanortricyclanol (−)-**16** (12%, 65% ee). Use of $TMSCH_2Li$ however, returned mainly unreacted starting epoxide **12** (68%). Remarkably, if the reaction of NBoc azanorbornene epoxide **12** with Pr^{i}Li in the presence of sparteine **2** was carried out in toluene instead of Et_2O, amino cyclohexenol **15** was not observed, and only azanortricyclanol (−)-**16** was isolated (50% yield, 75% ee). This last reaction underlines the strong influence of solvent on product profile with this substrate. In the reactions of azanorbornene epoxide **12** with Bu^{n}Li and Pr^{i}Li in Et_2O, the observations of different ees for the amino cyclohexenol **14**/**15** and the NBoc azanortricyclanol **16** provide further examples of enantiomeric partitioning:[12,14] in the presence of the chiral ligand sparteine, the relative proportions of the enantiomeric α-lithiated epoxides of **12** proceeding to **14**/**15** and **16** are different.

Given the earlier dependence on the nitrogen protecting group of reaction efficiency (both in terms of yield and asymmetric induction) in the desymmetrisations of 3,4-epoxytetrahydropyrroles, it was of interest to examine the corresponding NBus azanorbornene epoxide **19** (Scheme 5).



Scheme 4.



Scheme 5. Reagents and conditions: (i) TFA, CH_2Cl_2, 25 °C, 4 h; (ii) Et_3N, 25 °C, CH_2Cl_2, 1 h, then Bu^{t}SOCl, CH_2Cl_2, 0 °C, 1 h; (iii) CF_3COCH_3, Na_2EDTA, $NaHCO_3$, oxone, MeCN, 0 °C, 1.5 h; (iv) Bu^{n}Li or Pr^{i}Li, (−)-sparteine, Et_2O, −78 °C (5 h) to 25 °C (15 h).

The latter was prepared from the known NBoc azanorbornene **17**[21] via protecting group interchange. Thus, deprotection of NBoc azanorbornene **17** with TFA, followed by reaction of the TFA salt with Et_3N and Bu^{t}SOCl,[10] then oxidation of the resulting sulfinamide **18** using methyl(trifluoromethyl)dioxirane generated in situ[22] gave the desired NBus epoxide **19**. However, reaction of NBus epoxide **19** with Bu^{n}Li or Pr^{i}Li in the presence of sparteine in Et_2O gave lower yields and ees of amino cyclohexenols (−)-**20** (53%, 40% ee) and (−)-**21** (42%, 64% ee) respectively, compared to the corresponding NBoc systems (−)-**14** (55%, 67% ee) and (−)-**15** (78%, 87% ee). In Et_2O for NBus azanorbornene epoxide **19** (as with NBoc azanorbornene epoxide **12**), the corresponding NBus azanortricyclanol **16** (Bus=Boc) side-product was only detected (3%, 35% ee) when using Bu^{n}Li. We conclude that Boc protection is preferred to Bus protection for alkylative desymmetrisations in the aza bridged system (where bridgehead deprotonation is unlikely).

To study the substrate scope of the alkylative ring-opening process of 7-azabicyclo[2.2.1]heptyl systems we selected three other substrates for examination (Fig. 2). Potentially competing transannular C–H insertion was considered to be unlikely for acetal epoxide **22**, due to the additional strain that would arise from the presence of the acetal, and would not be possible for systems **23** and **24**. Also, alkylative desymmetrisation of substrates such as acetal epoxide **22** could potentially result in a new strategy to substituted aminocyclitols, which are an important group of bioactive compounds.[23]

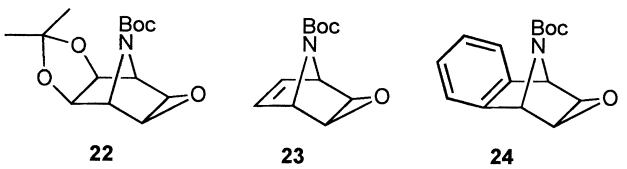
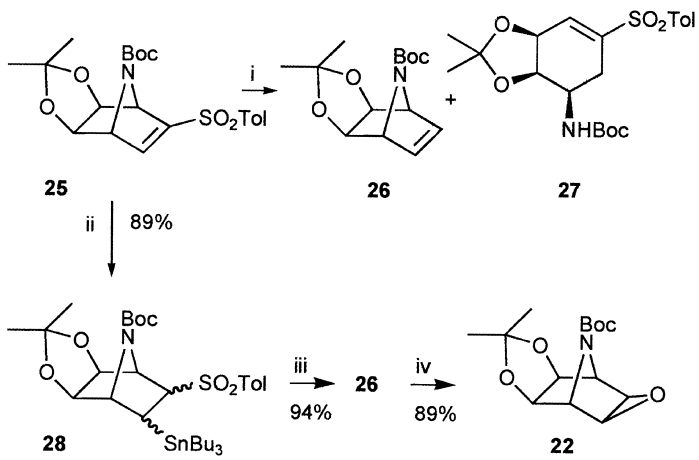


Figure 2. Desymmetrisation substrates **22**–**24**.

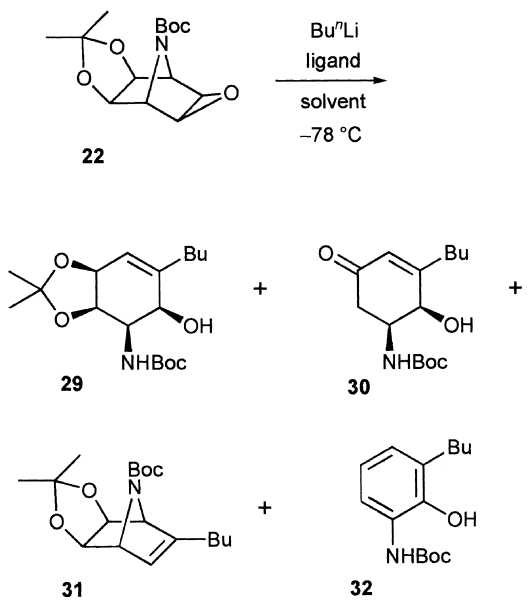
The synthesis of acetal-substituted epoxide **22** commenced with known sulfone **25** (Scheme 6), which is readily prepared in 3 steps via cycloaddition of commercially available NBoc pyrrole and tosyl ethyne.[24] Direct desulfonylation of sulfone **25** to give alkene **26**, the immediate precursor to epoxide **22**, was initially attempted using sodium amalgam. However, examination of typical desulfonylation conditions using 6% Na–Hg, with or without buffer [MeOH–THF (1:1), −20 °C (18 h);[25] NaH_2PO_4/Na_2HPO_4, MeOH, −10 °C (1 h) to 0 °C (5 h)[26]] led to inseparable mixtures of the desired alkene **9** together with the known[24] cyclohexene sulfone **27** (**26**:**27**, 1:0.6 and 1:3.6, respectively); **27** likely arises from electron transfer to the double bond in sulfone **25**, followed by aza-bridge opening. When boric acid was used as an additive[27] (MeOH, 25 °C, 5 h), very little of the unwanted cyclohexene sulfone **27** was observed; however, the desired alkene **26** was contaminated with substantial aromatic impurities.

We therefore applied a two-step procedure which has been successfully used to desulfonylate the corresponding 7-azabicyclo[2.2.1]heptene system lacking the acetal.[28] Pleasingly, addition of Bu_3SnH to sulfone **25** followed by fluoride-induced elimination in the resulting stannane **28** efficiently delivered alkene **26** (84% over two steps). Epoxidation of alkene **26** using MCPBA was very slow, and the epoxidation was best effected using in situ generated methyl(trifluoromethyl)dioxirane[22] to give the desired epoxide **22** in excellent yield (89%). The *exo*-selectivity in the epoxidation was assigned by analogy with epoxide **12**.[21]

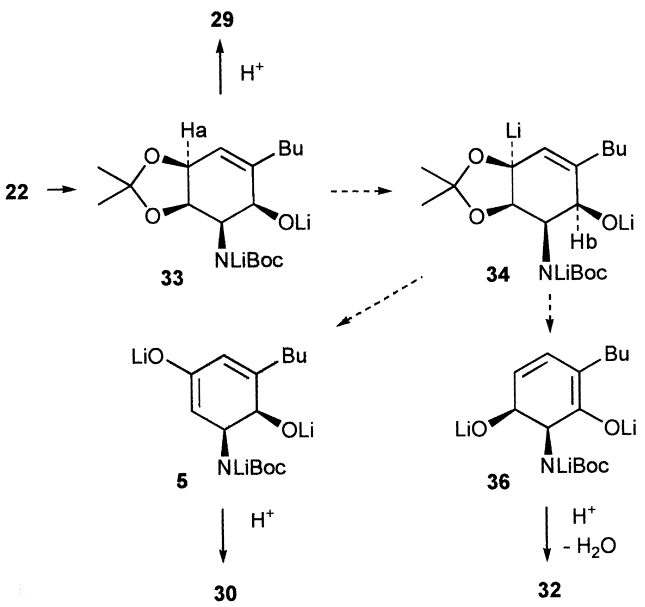
With an efficient route to epoxide **22** developed, we initiated desymmetrisation studies (Scheme 7, Table 1). Surprisingly, addition of epoxide **22** to Bu^{n}Li (3.5 equiv.) in THF at −78 °C, followed after 5 h at −78 °C by warming to 0 °C (1 h), led to one major product, aminophenol **32** [41%, Table 1, entry 1, **32** displays ^{1}H NMR spectral data (δ and J values) in the 8.2–6.5 region which are essentially identical to that reported[29] for the analogous aminophenol bearing a methyl instead of a butyl substituent; possible reaction pathways leading to **32** are discussed below]. In contrast, under otherwise identical reaction conditions but using Et_2O as solvent gave only a low recovery of starting epoxide **22** (19%, entry 2). With toluene as solvent the sought-after amino alcohol **29** was isolated, but only in low yield (11%, 30% brsm, entry 3). Also isolated from the reactions in THF and toluene was alkene **31** (5 and 17%, respectively).



Scheme 6. Reagents and conditions: (i) 6% Na–Hg; (ii) Bu_3SnH, AIBN, toluene, 80 °C, 1 h; (iii) TBAF, THF, reflux, 2 h; (iv) CF_3COCH_3, Na_2EDTA, $NaHCO_3$, oxone, MeCN, 0 °C, 2.5 h.



Scheme 7.



Scheme 8.

Table 1. Reaction of epoxide **22** with Bu^{n}Li (3.5 equiv.) at −78 °C

Entry	Ligand	Solvent	Recovered **22** (%)	**29** (%)	**30** (%)	**31** (%)	**32** (%)
1	—	THF	7	—	—	5	41
2	—	Et_2O	19	—	—	—	—
3	—	Toluene	37	11	—	17	—
4	**2**	Et_2O	7	16	16	7	10
5[a]	**2**	Et_2O	66	20[b]	—	—	—
6	**4**	Et_2O	24	—	—	—	52
7	**2**	Toluene	15	45[c]	9	—	—
8[a]	**2**	Toluene	36	41[d]	—	—	—
9	**4**	Toluene	37	11[e]	—	13	19
10	**2**	Cumene	5	35[f]	27	3	—

[a] Reaction quenched after 5 h at −78 °C.
[b] 70% ee.
[c] 72% ee.
[d] 76% ee.
[e] −67% ee.
[f] 71% ee.

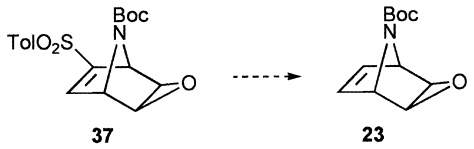
Alkene **31** is likely derived from the common α-lithiated epoxide intermediate (cf. Scheme 1) which also leads to the desired amino alcohol **29**; however, following intermolecular trapping by BuLi, elimination of Li_2O occurs. Although this latter process is a well-known reaction pathway for simple epoxides with organolithiums,[4] elimination of the uncharged NBoc group (with concomitant relief of ring strain) is normally strongly preferred in substrates structurally related to epoxide **22**, such as **12**.

In organolithium-mediated desymmetrisation reactions of achiral epoxides, the presence of a chiral ligand often exerts a significant influence on product profile, as well as inducing enantioselectivity.[4] Reaction under the above conditions in Et_2O but with (−)-sparteine **2** present (3.5 equiv.) led to a mixture of the desired amino alcohol **29** (16%), enone **30** (16%), bicyclic alkene **31** (7%) and aminophenol **32** (10%) (Table 1, entry 4). Enone **30** likely originates from the intermediate **33** which leads on protonation to **29** (Scheme 8). Deprotonation at the activated allylic acetal position (loss of Ha) in intermediate **33** leads to lithiated acetal **34**. Cycloelimination[30] (loss of acetone) from lithiated acetal **34** would give cross-conjugated enolate **35**, which generates enone **30** on work-up. When an otherwise identical reaction was carried out, but quenched after 5 h at −78 °C (rather than allowing it to warm-up), then only the desired amino alcohol (−)-**29** was isolated, albeit in low yield (20, 59% brsm, entry 5); this suggests that the undesired products derive from less selective reactions during the warm-up period. The ee of (−)-**29** from this latter reaction was determined to be 70%, which encouraged further studies. Intriguingly, under otherwise standard conditions but using bisoxazoline **4** as ligand in Et_2O led only to isolation of aminophenol **32** (52, 69% brsm, entry 6). Aminophenol **32** could potentially also arise from lithiated acetal **34** via an alternative (α-elimination) pathway which reveals its carbenoid[31] character; an ensuing (alkoxide-assisted) 1,4-hydride shift of Hb generates extended enolate **36** which leads to aminophenol **32** following loss of water on work-up. In an attempt to probe if **33** could be a potential intermediate en route to enone **30** and/or aminophenol **32**, amino alcohol **29** was treated with Bu^{n}Li (3.5 equiv., THF) which, however, led to an unidentifiable mixture of products.

Previous studies on enantioselective alkylative double ring-opening of epoxides derived from 8-oxabicyclo[3.2.1]-octenes indicated that switching from Et_2O to aromatic hydrocarbon solvents resulted in improved yields of cycloheptene diols.[14] In the present case under standard conditions with (−)-sparteine **2** present and using toluene as solvent led to a significant improvement in yield of the desired amino alcohol (−)-**29** (45% yield, 53% brsm, 72% ee; Table 1, entry 7), compared to the corresponding reaction in Et_2O (16% of **29**, entry 4). The desired reaction was clearly more rapid in toluene than Et_2O, as evidenced by quenching a sparteine-assisted reaction in toluene after 5 h at −78 °C: this resulted in formation of amino alcohol (−)-**29** (41%, 64% brsm, entry 8) in better conversion than the corresponding reaction in Et_2O (20%, 59% brsm, entry

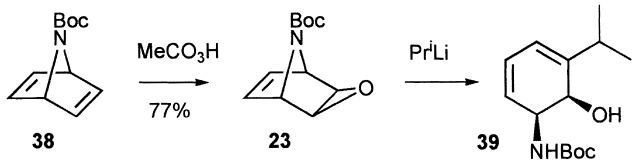
5). The ee of **29** was also slightly improved in toluene (76%) compared to Et_2O (70%). The conversion of epoxide **22** to amino alcohol **29** in toluene was not improved by extending the reaction time (17 h at −78 °C). Use of bisoxazoline **4** as ligand in toluene gave small amounts of (+)-**29** and alkene **31** (13%), along with the aminophenol **32** (19%, entry 9) which was also observed using **4** in Et_2O but to a greater extent (53%, entry 6). Cumene was briefly examined as an alternative solvent with (−)-sparteine **2** (entry 10); however, under otherwise standard conditions this led to a slightly lower yield of **29** with essentially the same ee to that seen in toluene (entry 7), and in cumene the enone **30** was a significant byproduct (27%). Attempted reaction of acetal epoxide **22** with Pr^{i}Li/sparteine **2** in toluene led to a mixture of unidentifiable products; whereas, similarly to epoxide **12**, no reaction was observed between acetal epoxide **22** and $TMSCH_2Li$/sparteine **2** in toluene.

In order to examine unsaturated epoxide **23**, its preparation was attempted by desulfonylation of known epoxide **37**[32] using sodium amalgam, and also by the Bu_3SnH-TBAF protocol [Bu_3SnH (1.5 equiv.), AIBN, toluene, 90 °C, 2 h followed by TBAF (12 equiv.), THF][28] (Scheme 9). However, these procedures gave the impure unsaturated epoxide **23** in low yield; moreover **23** could not be purified further by repeated column chromatography.



Scheme 9.

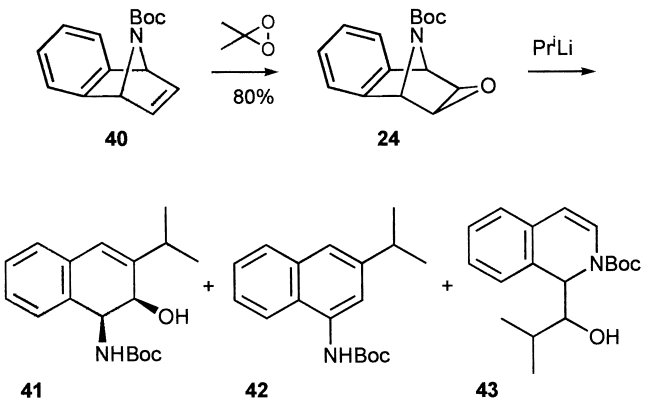
A more successful approach to unsaturated epoxide **23** involved monoepoxidation of the known diene **38**[33] (Scheme 10). Whilst epoxidation of diene **38** using peracetic acid was slow (36 h), it gave pure unsaturated epoxide **23** in 77% yield, without any evidence for di-epoxidation.



Scheme 10.

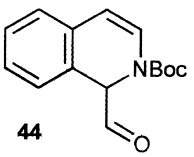
Reaction of unsaturated epoxide **23** with Pr^{i}Li in Et_2O gave the desired amino alcohol **39**, albeit in low yield (22%) along with a number of other products which were not identified; in the presence of sparteine **2**, the yield of amino alcohol **39** increased slightly to 32% and **39** was generated in good ee (79%). Due to the low yields of **39** obtained, however, further investigation of this substrate was not pursued and efforts focused on the more available benzo-epoxide **24** (Scheme 11).

Benzo-epoxide **24** was synthesised from the cycloadduct **40** of NBoc pyrrole and benzyne[34] by epoxidation using dimethyldioxirane generated in situ (80%).[35] Reaction of benzo-epoxide **24** with Pr^{i}Li in Et_2O was examined in the

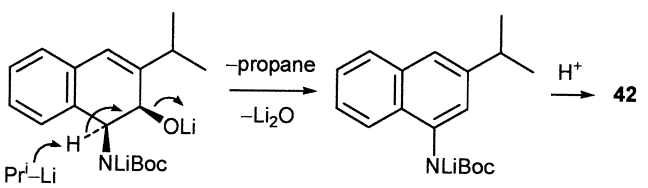


Scheme 11.

absence of a ligand, and with added TMEDA and sparteine, and provided another example of significant ligand affects on product profile. For Pr^{i}Li (2 equiv.) in the absence of a ligand, the desired amino alcohol **41** was obtained in 32% yield. The reaction also yielded several other products, among which the naphthylamine **42** (6%) and the dihydro-isoquinolinol **43** (17%) were isolated; possible reaction pathways leading to **42** and **43** are discussed below. Use of Pr^{i}Li/TMEDA (3 equiv. each) was found to give exclusively naphthylamine **42** (65%), whereas with Pr^{i}Li/sparteine **2** (3 equiv. each), a mixture of the amino alcohol **41** (44%, 71% ee) and naphthylamine **42** (41%) were obtained. On reducing the equivalents of organolithium/(−)-sparteine used (from **3** to **2**), amino alcohol **41** was formed in slightly lower yield (30%), and the amount of naphthylamine **42** formed was reduced more significantly (from 41 to 14%), but an additional product was also isolated, aldehyde **44** (33%).



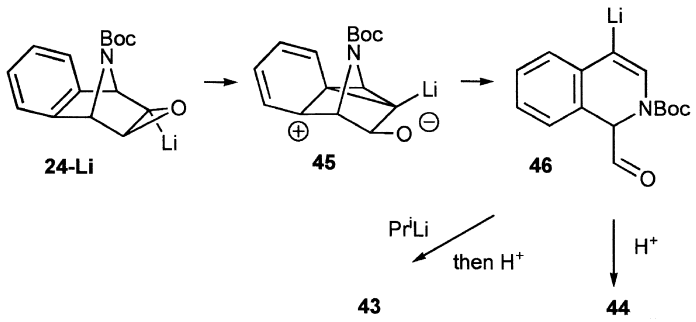
The naphthylamine **42** is likely derived from the amino alcohol **41** by elimination/dehydration. The amino alcohol **41** was shown to be stable to the acidic conditions used for work-up, but when **41** was treated with Pr^{i}Li (3 equiv., Et_2O, −78 °C), a quantitative yield of the naphthylamine **42** was obtained. These observations suggest aromatisation to **42** occurs with concomitant formation of Li_2O (*eg.* Scheme 12).



Scheme 12.

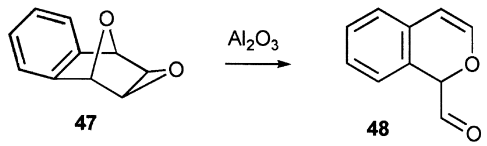
Suggested reaction pathways for the formation of dihydro-isoquinolinol **43** and aldehyde **44** are more speculative (Scheme 13).

π-Participation from the aromatic ring may assist C–O



Scheme 13.

cleavage of the electrophilic[31] lithiated epoxide **24**-Li to give **45**; fragmentation of **45** could then lead to lithiated aldehyde **46** from which aldehyde **44** arises on protonation, and dihydroisoquinolinol **43** (as a 1:1 mixture of rotational isomers or diastereoisomers) via addition of Pr^{i}Li. French and Charlton have reported a related rearrangement of the benzyne–furan cycloadduct-derived epoxide **47** to aldehyde **48** using acidic alumina (Scheme 14).[36]



Scheme 14.

3. Conclusion

Enantioselective nucleophilic ring-opening of unsaturated oxa- and (to a lesser extent) aza-bicyclic compounds, principally being developed by Lautens,[37] results in cycloalkenes bearing the nucleophile in an allylic position. Proceeding via double ring-opening, the chemistry described herein comprises an intermolecular C–C single bond forming reaction with cogeneration of unsaturation and two functional group reorganizations, leading to nucleophile incorporation at a vinylic position and synthetically valuable 1,2-amino alcohol functionality. It provides a new and enantioselective access to sought-after cyclic unsaturated amino alcohols[8] in a regio-, stereo- and enantiocontrolled fashion, and thus has the potential to be a powerful method for organic synthesis. Extensions of the current process to other epoxides, organolithiums and manipulations of the adducts towards targets of biological interest are under investigation.

4. Experimental

4.1. General

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, pentane, hexane and toluene 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 fluorescent indicator (Merck). Column chromatography was carried out on Kieselgel 60 (40–63 mm). Petrol refers to the fraction with bp 40–60 °C. Melting points were determined using a Leica VMTG apparatus and are uncorrected. Elemental analyses were performed by Elemental Microanalysis Limited, Okehampton, Devon, UK. $[\alpha]_D$ Values are given in 10^{-1} deg. cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated with Bruker JEOL EX400 or Bruker AM500 spectrometers. Chemical shifts are reported relative to $CDCl_3$ [δ_H 7.26, δ_C (central line of triplet) 77.0]. Coupling constants (J) are given in Hz, to the nearest 0.5 Hz. Mass spectra were obtained by the EPSRC National Mass Spectrometry Service Centre at the University of Swansea, using a Micromass Quattro II low resolution triple quadrupole mass spectrometer or, for accurate masses, using a Finnigan MAT 900 XLT high resolution double focusing mass spectrometer with tandem Ion Trap. 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. Retention times for major (t_R mj) and minor (t_R mn) enantiomers are given in minutes.

4.1.1. 1,1-Dimethylethyl (2-hydroxy-3-methyleneheptyl)-carbamate 3.[6] To a solution of (−)-sparteine **2** (0.19 cm^3, 0.81 mmol) in Et_2O (1 cm^3) at −78 °C was added Bu^{n}Li (2.3 mol dm^{-3} in pentane; 0.35 cm^3, 0.81 mmol). After 1 h at −78 °C a solution of NBoc epoxide **1** (50 mg, 0.27 mmol) in Et_2O (8 cm^3) was added dropwise. After 1 h at −78 °C the reaction was warmed to 25 °C over 1 h and then sat. aq. NH_4Cl (5 cm^3) was added. The reaction mixture was extracted with Et_2O (3×10 cm^3) and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (15 cm^3), brine (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 30–60% Et_2O–petrol) gave amino alcohol **3** (17 mg, 25%) as a white solid; $[\alpha]_D^{23}$=+2.8 (c 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate (see Supporting information) was determined to be 45% by chiral HPLC (OD column, 10% Pr^{i}OH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 44.2; t_R mn, 53.9).

4.1.2. *N*-(2-Hydroxy-3-methyleneheptyl)-2-methyl-2-propanesulfonamide 6.[6] Following the above procedure for **3**, but using (−)-sparteine **2** (0.34 cm^3, 1.46 mmol),

Bu^nLi (2.5 mol dm^{-3} in hexanes; 0.59 cm^3, 0.15 mmol) and NBus epoxide **5** (100 mg, 0.49 mmol) gave amino alcohol **6** (89 mg, 69%) as a white solid; $[\alpha]_D^{23}=+4.4$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate (see Supporting information) was determined to be 24% by chiral HPLC (OD column, 10% Pr^iOH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 56.9; t_R mn, 75.1).

4.1.3. 1-[(1,1-Dimethylethyl)sulfonyl]-1*H*-pyrrole. 2,5-Dimethoxytetrahydrofuran (0.062 cm^3, 0.48 mmol) was added to a stirred suspension of P_2O_5 (91 mg, 0.32 mmol) and $Bu^tSO_2NH_2$[15] (45 mg, 0.32 mmol) in toluene (40 cm^3) at 25 °C. The mixture was then heated to 110 °C for 15 min (the time required for the reaction mixture to change colour from yellow to black). Aq. KOH (2 mol dm^{-3}; 1.25 cm^3) was then added and the organic layer was extracted with Et_2O (3×5 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 0–2.5% Et_2O–petrol) gave NBus pyrrole (53 mg, 88%) as a white crystalline solid; R_f 0.75 (40% Et_2O–petrol); mp 107–108 °C (Found: C, 51.8; H, 7.0; N, 7.1. $C_8H_{13}NSO_2$ requires C, 51.3; H, 7.0; N, 7.5%); ν_{max}(KBr)/cm^{-1} 2986, 1636, 1479, 1451, 1346, 1180, 1140, 1064 and 1035; δ_H (400 MHz) 7.08–7.07 (2H, m, NCH), 6.34–6.32 (2H, m, CH=) and 1.38 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 129.7 (NCH), 119.3 (CH=), 69.4 ($C(CH_3)_3$) and 31.5 ($C(CH_3)_3$); *m*/*z* [CI+(NH_3)] 205 ($M+NH_4^+$, 100%), 188 ($M+H^+$, 17), 118 (21) and 68 (45) (Found: $M+H^+$, 188.0749. $C_8H_{14}NSO_2$ requires 188.0745).

4.1.4. *N*-(2-Hydroxy-4-methyl-3-methylenepentyl)-2-methyl-2-propanesulfonamide 7.[6] Following the above procedure for **3**, but using (−)-sparteine **2** (0.34 cm^3, 1.46 mmol), Pr^iLi[38] (2.0 mol dm^{-3} in petrol; 0.73 cm^3, 1.46 mmol) and NBus epoxide **5** (100 mg, 0.49 mmol) gave amino alcohol **7** (48 mg, 39%) as a white solid; $[\alpha]_D^{23}=+3.6$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate was determined to be 46% by chiral HPLC (OD column, 10% Pr^iOH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 58.4; t_R mn, 72.2).

4.1.5. *N*-[2-Hydroxy-3-[(trimethylsilyl)methyl]-3-butenyl]-2-methyl-2-propanesulfonamide 8.[6] Following the above procedure for **3**, but using (−)-sparteine **2** (0.34 cm^3, 1.46 mmol), $TMSCH_2Li$ (1.00 mol dm^{-3} in pentane; 1.46 cm^3, 1.46 mmol) and NBus epoxide **5** (100 mg, 0.49 mmol) gave amino alcohol **8** (70 mg, 49%) as a white solid; $[\alpha]_D^{23}=+1.8$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate was determined to be 2% by chiral HPLC (OD column, 10% Pr^iOH in heptane, 0.5 cm^3 min^{-1}, t_R mj, 40.7; t_R mn, 59.7).

4.1.6. 1,1-Dimethylethyl [(1*R,2*S**)-2-hydroxy-(1-methylpropyl)-3-cyclohexen-1-yl]carbamate 13.** (−)-Sparteine **2** (1.14 cm^3, 5 mmol, 3.5 equiv.) was added dropwise to a stirred solution of Bu^sLi (1.3 mol dm^{-3} in cyclohexane; 3.8 cm^3, 5 mmol, 3.5 equiv.) in Et_2O (10 cm^3) at −78 °C. After 1 h, epoxide **12** (300 mg, 1.42 mmol) in Et_2O (4 cm^3) was added. The reaction mixture was stirred at −78 °C for 5 h and then slowly warmed to 25 °C over 10 h. 1 M HCl (5 cm^3) was added and the aqueous layer was extracted with Et_2O (3×20 cm^3). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O–petrol) gave amino cyclohexenol **13** (283 mg, 74%) as a colourless oil; R_f 0.36 (50% Et_2O–petrol); $[\alpha]_D^{24}=-52.8$ (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3438s, 2963s, 1690s, 1500s and 1360s; δ_H (500 MHz) 5.57–5.54 (1H, m, C=CH), 5.14 (1H, br s, NH), 4.01–3.98 (1H, m, C*H*OH), 3.62–3.60 (1H, m, C*H*NHBoc), 2.21–2.16 (2H, m, $=CH_2$), 2.08 (1H, ap. sxt, *J*=7.0, CH), 1.78–1.73 (1H, m, H of CH_2), 1.63–1.49 (2H, m, 2×H of CH_2), 1.47 (9H, s, Bu^t), 1.45–1.31 (1H, m, H of CH_2), 1.07 (1H, d, *J*=7.0 Hz, Me), 1.06 (2H, d, *J*=7.0 Hz, Me) and 0.86 (3H, t, *J*=7.5 Hz, Me); δ_C (125 MHz, 2:1 mixture of rotational isomers observed) 155.4 (C=O), 142.9 and 142.5 (*C*=CH, quat.), 124.5 and 124.1 (C=*C*H), 79.2 (CMe_3), 67.5 and 66.8 (CHOH), 50.9 (CHNH), 40.5 and 38.9 (CH of Bu^s), 29.2 and 28.2 (CH_2), 28.4 (3×Me), 24.8 ($=CH_2$), 23.0 and 22.9 (CH_2), 20.8 and 19.0 (Me) and 12.3 and 11.6 (Me); *m*/*z* (CI) 270 ($M+H^+$, 65%), 213(100) and 196 (65) (Found: $M+H^+$, 270.2069. $C_{15}H_{28}NO_3$ requires 270.2069).

Also isolated was NBoc azanortricyclanol **16**[21] (35 mg, 12%); $[\alpha]_D^{23}=-10.0$ (*c* 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate of **16** (see Supporting information) was determined to be 65% by chiral HPLC (OD column, 50% EtOH in hexane, 0.5 cm^3 min^{-1}, t_R mj, 18.9; t_R mn, 21.2).

4.1.7. 1,1-Dimethylethyl [(1*R,2*S**)-3-butyl-2-hydroxy-3-cyclohexen-1-yl]carbamate 14.** Following the above procedure for **13**, but using (−)-sparteine **2** (0.16 cm^3, 3 equiv.), Bu^nLi (2.5 mol dm^{-3} in hexanes; 0.28 cm^3, 0.72 mmol, 3 equiv.) and epoxide **12** (50 mg, 0.237 mmol) gave amino cyclohexenol **14** (35 mg, 55%) as a colourless oil; R_f 0.43 (50% Et_2O–petrol); $[\alpha]_D^{24}=-52.2$ (*c* 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3436br s, 2957s, 2931s, 1716s, 1691s, 1503s, 1367s and 1169s; δ_H (400 MHz) 5.55 (1H, br s, C=CH), 5.12–5.10 (1H, br d, *J*=7.5 Hz, NH), 3.96 (1H, br s, C*H*OH), 3.66–3.61 (1H, m, C*H*NHBoc), 2.17–2.05 (4H, m, 2×CH_2), 1.75–1.51 (4H, m, 2×CH_2), 1.46 (9H, s, Bu^t), 1.43–1.25 (2H, m, CH_2) and 0.90 (3H, t, *J*=7.0 Hz, Me); δ_C (100 MHz) 155.5 (C=O), 138.3 (HC=*C*, quat.), 125.0 (*C*H=C), 79.2 (CMe_3), 67.8 (CHOH), 50.7 (CHNH), 34.1 (CH_2 of Bu^n), 30.3 (CH_2), 28.4 (3×Me), 24.7 (CH_2), 23.0 (CH_2 of Bu^n), 22.5 (CH_2 of Bu^n) and 14.0 (Me of Bu^n); *m*/*z* (CI) 270 ($M+H^+$, 5%), 214 (10), 196 (55), 170 (M−Boc, 15) and 152 (100) (Found: $M+H^+$, 270.2064. $C_{15}H_{28}NO_3$ requires 270.2069). The ee of the 3,5-dinitrobenzoate of **14** (see Supporting information) was determined to be 67% by chiral HPLC (OD column, 15% EtOH in hexane, 0.5 cm^3 min^{-1}, t_R mj, 14.1; t_R mn, 22.4).

Also isolated was NBoc azanortricyclanol **16**[21] (7 mg, 14%, 35% ee); $[\alpha]_D^{24}=-3.0$ (*c* 1.0 in $CHCl_3$).

4.1.8. 1,1-Dimethylethyl [(1*R,2*S**)-2-hydroxy-3-(1-methylethyl)-3-cyclohexen-1-yl]carbamate 15.** Following the above procedure for **13**, but using (−)-sparteine **2** (0.95 cm^3, 4.1 mmol, 3.5 equiv.), Pr^iLi[38] (1.4 mol dm^{-3} in petrol; 3.0 cm^3, 4.2 mmol, 3.5 equiv.) and epoxide **12** (250 mg, 1.2 mmol) gave amino cyclohexenol **15** (240 mg, 78%) as a white solid; R_f 0.55 (50% Et_2O–petrol); $[\alpha]_D^{24}=-65.0$ (*c* 1.0 in $CHCl_3$); mp 77.5–80.5 °C (from Et_2O–petrol) (Found: C, 65.8; H, 9.8; N, 5.5.

$C_{14}H_{25}NO_3$ requires C, 65.85; H, 9.9; N, 5.5%); ν_{max}(KBr)/cm^{-1} 3437br s, 2960s, 1691s, 1501s and 1367s; δ_H (500 MHz) 5.56 (1H, t, J=3.5 Hz, C=CH), 5.15 (1H, d, J=8.0 Hz, NH), 4.03 (1H, d, J=2.5 Hz, C*H*OH), 3.62–3.58 (1H, m, C*H*NHBoc), 2.38 (1H, septet, J=7 Hz, CH of Pr^i), 2.19–2.08 (2H, m, =CH_2), 1.81–1.69 (1H, m, H of CH_2), 1.60–1.51 (1H, m, H of CH_2), 1.45 (9H, s, Bu^t), 1.06 (3H, d, J=7.0 Hz, Me) and 1.03 (3H, d, J=7.0 Hz, Me); δ_C (125 MHz) 155.5 (C=O), 144.1 (HC=*C*, quat.), 122.9 (H*C*=C), 79.2 (*C*Me_3), 67.0 (CHOH), 50.8 (CHNH), 32.1 (CH of Pr^i), 28.4 (3×Me), 24.7 (=CH_2), 22.9 (Me), 22.6 (Me) and 21.6 (CH_2); m/z (CI) 256 ($M+H^+$, 5%), 156 (5) and 138 (100) (Found: $M+H^+$, 256.1911. $C_{14}H_{26}NO_3$ requires 256.1912). The ee of the 2,4-dinitrobenzoate (see Supporting information) was determined to be 87% by chiral HPLC (AD Column, 50% EtOH in hexane, 1.0 cm^3 min^{-1}, t_R mj, 4.0; t_R mn, 10.0).

4.1.9. 7-(2-Methylpropane-2-sulfinyl)-7-azabicyclo-[2.2.1]hept-2-ene 18. TFA (0.75 cm^3, 9.7 mmol) was added to a solution of alkene **17**[21] (100 mg, 0.51 mmol) in CH_2Cl_2 (7 cm^3) at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. The solvent was removed under reduced pressure and the residue azeotroped with toluene (3×15 cm^3) to give the TFA salt as a dark coloured oil (150 mg, >100%); ν_{max}(film)/cm^{-1} (very broad peaks) 3420 m, 2967 s, 1780 s and 1672 s; δ_H (200 MHz) 8.50 (1H, br s, NH.TFA), 8.20 (1H, br s, NH.TFA), 6.28 (2H, s, HC=CH), 4.63 (2H, s, 2×CH), 2.15 (2H, br d, J=8.5 Hz, 2×H of CH_2) and 1.38 (2H, br d, J=8.5 Hz, 2×H of CH_2). To a solution of the above TFA salt (0.10 g, 0.48 mmol) in CH_2Cl_2 (3 cm^3) at 25 °C was added Et_3N (0.670 cm^3, 4.80 mmol) dropwise. After 1 h, the reaction was cooled to 0 °C and a solution of ice-cold Bu^tSOCl[10] (0.135 g, 0.96 mmol) in CH_2Cl_2 (2 cm^3) was added. After a further 1 h, the mixture was diluted with sat. aq. $NaHCO_3$ (3 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3×5 cm^3) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 0–30% Et_2O–petrol) gave the sulfinamide **18** (95 mg, quant.) as a clear colourless oil; R_f 0.25 (30% Et_2O–petrol); ν_{max}(film)/cm^{-1} 2949, 2866, 1589, 1476, 1457, 1360, 1311, 1187, 1077 and 981; δ_H (200 MHz) 7.28 (1H, dd, J=6.0, 2.0 Hz, CH=), 6.16 (1H, dd, J=6.0, 2.0 Hz, CH=), 4.45 (1H, br, s, NCH), 4.33 (1H, br, s, NCH), 2.05–1.80 (2H, m, 2×CH of CH_2), 1.30–1.13 (11H, m, 2×CH of CH_2, $C(CH_3)_3$); δ_C (50 MHz) 136.8 (CH=), 132.9 (CH=), 64.4 (NCH), 61.6 (NCH), 57.5 ($C(CH_3)_3$), 25.3 (CH_2), 23.7 (CH_2) and 22.7 ($C(CH_3)_3$); m/z[CI+(NH_3)] 202 (20%), 200 ($M+H^+$, 100), 184 (17), 112 (22), 100 (22), 98 (55), 96 (87) and 72 (22) (Found: $M+H^+$, 200.1109. $C_{10}H_{18}NOS$ requires 200.1109).

4.1.10. 8-(2-Methylpropane-2-sulfonyl)-8-aza-3-oxatricyclo[3.2.1.0^{2,4}]octane 19. To a solution of sulfinamide **18** (0.42 g, 2.11 mmol) and Na_2EDTA (4×10^{-4} mol dm^{-3} in H_2O; 10.6 cm^3, 0.004 mmol) in MeCN (15 cm^3) at 0 °C was added trifluoroacetone (2.10 cm^3, 23.4 mmol) dropwise. A mixture of $NaHCO_3$ (1.36 g, 16.2 mmol) and oxone (6.43 g, 10.1 mmol) was then added portionwise over 1 h. After 1.5 h the reaction mixture was filtered, the filtrate was diluted with H_2O (50 cm^3) and extracted with CH_2Cl_2 (3×30 cm^3). The combined organic layers were washed with sat. aq. sodium bisulfite, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 0–100% Et_2O–petrol) gave NBus azanorbornene epoxide **19** (0.38 g, 78%) as a white crystalline solid; R_f 0.33 (30% Et_2O–petrol); mp 104.5–105 °C; (Found: C, 51.7; H, 7.0; N, 7.1. $C_{10}H_{17}NO_3S$ requires C, 51.3; H, 7.0; N, 7.5%); ν_{max}(KBr)/cm^{-1} 3435, 2982, 2875, 1591, 1478, 1319, 1215, 1147, 1122 and 1050; δ_H (400 MHz) 4.16–4.15 (2H, m, 2×NCH), 3.27 (2H, s, 2×OCH), 1.88 (2H, d, J=5.0 Hz, 2×CH_{exo} of CH_2), 1.51 (2H, dd, J=5.0, 13.0 Hz, 2×CH_{endo} of CH_2) and 1.35 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 60.4 (NCH), 60.1 ($C(CH_3)_3$), 26.4 (CH_2), and 23.9 ($C(CH_3)_3$); m/z [CI+(NH_3)] 249 ($M+NH_4^+$, 100), 233 (23), 216 (20), 112 (28), 100 (20), 96 (24) and 74 (17) (Found: $M+NH_4^+$, 249.1273. $C_{10}H_{21}N_2O_3S$ requires 249.1273).

4.1.11. *N*-[(1*R* *,2*S* *)-3-Butyl-2-hydroxy-3-cyclohexen-1-yl]-2-methyl-2-propanesulfonamide 20. To a stirred solution of (−)-sparteine **2** (0.15 cm^3, 0.65 mmol) in Et_2O (1 cm^3) at −78 °C was added Bu^nLi (2.3 mol dm^{-3} in hexanes; 0.28 cm^3, 0.65 mmol). After 1 h at −78 °C a solution of NBus azanorbornene epoxide **19** (50 mg, 0.22 mmol) in Et_2O (2.5 cm^3) was added and after 5 h at −78 °C the reaction was warmed to 25 °C overnight. Sat. aq. NH_4Cl (5 cm^3) was added to the reaction mixture which was then extracted with Et_2O (3×10 cm^3) and the combined organic layers washed with sat. aq. $NaHCO_3$ (15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 30–60% Et_2O–petrol) gave amino alcohol **20** (32 mg, 53%) as a white solid; R_f 0.30 (50% Et_2O–petrol); mp 97–98.5 °C; $[\alpha]_D^{23}$=−22.3 (c 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3484, 3011, 2995, 2991, 2852, 1736, 1735, 1631, 1594, 1583, 1642, 1408, 1400, 1374, 1271, 1122, 1100, 1068 and 977; δ_H (400 MHz) 6.56–6.52 (1H, m, =CH), 4.65 (1H, br, d, J=10.0 Hz, NH), 4.04–4.00 (1H, m, CHO), 3.47–3.39 (1H, m, CHN), 2.16–2.04 (4H, m, =CHCH_2, CH_2C=), 1.83–1.66 (2H, m, CH_2CHN), 1.66–1.27 (13H, m, $CH_3CH_2CH_2$, CH_3CH_2, $C(CH_3)_3$) and 0.90 (3H, t, J=7.0 Hz, CH_2CH_3); δ_C (100 MHz) 138.3 (C=), 124.6 (=CH), 68.7 (CHO), 59.6 ($C(CH_3)_3$), 55.3 (CHN), 34.1 (CH_2C=), 30.2 ($CH_3CH_2CH_2$), 25.0 (=CHCH_2), 24.3 (CH_2CHN), 24.2 ($C(CH_3)_3$), 22.5 (CH_3CH_2) and 14.2 ($CH_3(CH_2)_3$); m/z [CI+(NH_3)] 307 ($M+NH_4^+$, 100%), 291 (28), 272 (32), 249 (30), 170(25), 155 (56), 137 (25) and 52 (27) (Found: $M+NH_4^+$, 307.2058. $C_{14}H_{31}N_2O_3S$ requires 307.2055). The ee of the 3,5-dinitrobenzoate (see Supporting information) was determined to be 40% by chiral HPLC (OD column, 15% EtOH in hexane, 0.5 cm^3 min^{-1}, $t_R$mn, 15.6; $t_R$mj, 25.2).

Also isolated was NBus azanortricyclanol **16** (Bus=Boc) (1.5 mg, 3%): R_f 0.20 (50% Et_2O in petrol); $[\alpha]_D^{23}$=−7.7 (c 1.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3463, 3010, 2982, 1463, 1420, 1402, 1371, 1206, 1111, 1006 and 964; δ_H (500 MHz) 3.98 (1H, s, CHO), 3.75 (1H, s, NC*H*CH_2), 3.49 (1H, dd, J=4.5, 4.5 Hz, NC*H*CHCH_2), 1.66 (2H, s, CH_2), 1.64–1.60 (2H, m, NHCHC*H*CH_2, OH), 1.54–1.49 (1H, m, OCHC*H*CH) and 1.46 (9H, s, $C(CH_3)_3$); δ_C (100 MHz) 77.0 ($C(CH_3)_3$), 75.7 (CHO), 60.5 (N*C*HCH_2), 35.8 (N*C*HCH), 30.8 (CH_2), 24.2 (($CH_3)_3$C), 17.8 (OCH*C*HCH)

and 14.6 (NHCH*C*HCH$_2$); *m*/*z*[CI+(NH$_3$)] 249 (M+NH$_4^+$, 64%), 232 (M+H$^+$, 100), 192 (19), 190 (57), 173 (41), 155 (25), 152 (12), 112 (49), 110 (84), 108 (16), 96 (11), 94 (22), 86 (17) and 80 (16) (Found: M+H$^+$, 232.1006. $C_{10}H_{18}NO_3S$ requires 232.1007). The ee of the 3,5-dinitrobenzoate derivative (see Supporting information) was determined to be 35% by chiral HPLC (OD column 50% EtOH in hexane, 0.5 cm^3 min^{-1}, $t_R$mj, 26.4; $t_R$mn, 32.9).

4.1.12. *N*-[(1*R* *,2*S* *)-2-hydroxy-3-(1-methylethyl)-3-cyclohexen-1-yl]-2-methyl-2-propanesulfonamide 21. Following the procedure for amino alcohol **20** above, but using (−)-sparteine **2** (0.13 cm^3, 0.57 mmol), Pr^{i}Li[38] (1.1 mol dm^{-3} in petrol; 0.53 cm^3, 0.58 mmol) and NBus azanorbornene epoxide **19** (44 mg, 0.19 mmol) gave amino alcohol **21** (21 mg, 42%) as a white solid; R_f 0.13 (50% Et$_2$O–petrol); mp 95–95.5 °C; $[\alpha]_D^{23}=-56$ (*c* 1.0 in CHCl$_3$); ν_{max}(KBr)/cm^{-1} 3460, 3277, 2957, 2872, 2839, 1457, 1395, 1365, 1300, 1212, 1187, 1167, 1126, 1081, 1064, 1032 and 992; δ_H (400 MHz) 5.58 (1H, t, *J*=3.0 Hz, =CH), 4.75–4.63 (1H, m, NH), 4.13–4.06 (1H, m, CHO), 3.45–3.37 (1H, m, CHN), 2.36 (1H, septet, *J*=6 Hz, C*H*(CH$_3$)$_2$), 2.34–2.08 (2H, m, =CHC*H*$_2$), 1.86–1.67 (2H, m, NHCHC*H*$_2$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.06 (3H, d, *J*=7.0 Hz, CHC*H*$_3$) and 0.85 (3H, dd, *J*=7.0, 14.5 Hz, CHC*H*$_3$); δ_C (100 MHz) 144.1 (C=), 122.6 (=CH), 67.9 (CHO), 65.8 (*C*(CH$_3$)$_3$), 55.5 (CHN), 32.2 (*C*H(CH$_3$)$_2$), 24.8 (*C*H$_2$CHN), 24.2 (*C*H$_2$C=), 22.6 ((*C*H$_3$)$_3$C) and 21.7 (*C*H$_3$)$_2$CH); *m*/*z* [CI+(NH$_3$)] 293 (M+NH$_4^+$, 91%), 275 (14), 258 (100), 155 (23), 138 (39) and 123 (31) (Found: M+NH$_4^+$, 293.1900. $C_{13}H_{29}N_2O_3S$ requires 293.1899). The ee of the 3,5-dinitrobenzoate derivative (see Supporting information) was determined to be 64% by chiral HPLC (OD column, 15% EtOH in hexane, 0.5 cm^3 min^{-1}, $t_R$mn, 21.4; $t_R$mj, 25.4).

4.1.13. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-5-tributylstannyl-3a,4,5,6,7,7a-octahydro-2,2-dimethyl-5-[(4-methylphenyl)sulfonyl]-1,3-benzodioxol-4,7-imine-8-carboxylate 28. BuSn$_3$H (2.604 g, 8.9 mmol) and AIBN (0.04 g, 0.24 mmol) were added to a solution of alkene **25**[24] (1.523 g, 3.6 mmol) in toluene (16 cm^3) and the mixture heated to 80 °C. After 1 h the reaction mixture was cooled, adsorbed onto SiO$_2$ and purified by column chromatography (20% EtOAc–petrol) to give a mixture of stannanes **28** (2.281 g, 89%) as a colourless oil; R_f 0.61 (20% EtOAc–petrol); ν_{max}/cm^{-1} 3438br, m, 2958s, 2928s, 2872m, 1704s, 1597w, 1403s, 1323m, 1261m, 1210m, 1148s, 1107m, 1088 m, 1064 m, 901m, 813m, 733m, 668s and 584s; δ_H (200 MHz) 7.75 (2H, d, *J*=8 Hz, Ar), 7.35 (2H, d, *J*=8 Hz, Ar), 5.20 (1H, ap. d, *J*=5.5 Hz, 6-H), 4.35 (1H, ap. d, *J*=5.5 Hz,), 4.30–4.18 (2H, m), 3.63–3.45 (1H, m), 2.45 (3H, s, Ar*Me*), 1.43 (9H, s, OCMe$_3$), 1.70–1.15 (25H, m) and 0.89 (9H, t, *J*=7 Hz, 3×CH$_2$*Me*); δ_C (100 MHz) 145.2, 130.3, 127.9, 110.0, 83.3, 80.2, 77.6, 63.3, 60.1, 28.9, 28.4, 27.4, 25.5, 21.6, 13.7 and 9.0; *m*/*z* [CI+(NH$_3$)] 714 (M+H$^+$, 100%), 713 (M$^+$, 50), 712 (70) and 710 (35) (Found: M+H$^+$, 714.2862. $C_{33}H_{56}NO_6S^{120}Sn$ requires 714.2850).

4.1.14. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4,7-imine-8-carboxylate 26. TBAF (1 mol dm^{-3} in THF; 10 cm^3, 0.01 mol) was added to a solution of **28** (3.0 g, 4.2 mmol) in THF (25 cm^3) and the mixture then heated under reflux. After 2 h the reaction mixture was cooled and evaporated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–petrol) gave alkene **26** (1.057 g, 94%) as a white solid; R_f 0.3 (20% EtOAc–petrol); mp 63–65 °C; ν_{max}/cm^{-1} 2797m, 2936m, 1704s, 1369m, 1209m, 1159s, 1112m, 1089w, 1060m, 882w and 857w; δ_H (400 MHz, 2 rotamers observed) 6.34 and 6.29 (2H, two m, 5,6-H), 4.72 and 4.63 (2H, two m, 4,7-H), 4.28 (2H, s, 3a,7a-H), 1.48 (3H, s, Me), 1.46 (9H, s, OCMe$_3$) and 1.31 (3H, s, Me); δ_C (100 MHz) 154.4 (C=O), 136.7 and 135.5 (C5, C6), 115.8 (Me$_2$*C*O$_2$), 79.8 (O*C*Me$_3$), 79.8 and 79.4 (C3a, C7a), 62.8 and 62.1 (C4, C7), 28.3 (OC*Me*$_3$), 25.2 (Me) and 23.3 (Me); *m*/*z* [Cl$^+$] 268 (M+H$^+$, 25%), 169 (100), 100 (40) and 85 (18) (Found: M+H$^+$, 268.1553. $C_{14}H_{22}NO_4$ requires 268.1549).

4.1.15. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-3a,4,7,7a-octahydro-2,2-dimethyl-1,3-benzodioxol-5,6-oxiren-4,7-imine-8-carboxylate 22. Na$_2$EDTA (4×10^{-4} mol dm^{-3} in H$_2$O; 20 cm^3, 0.008 mmol) was added to a solution of alkene **26** (1.057 g, 3.96 mmol) in MeCN (29 cm^3). The resulting homogeneous solution was cooled to 0 °C, followed by addition of trifluoroacetone (4 cm^3, 45 mmol). To this solution a mixture of NaHCO$_3$ (2.4 g, 29 mmol) and oxone (11.2 g, 18 mmol) was added in portions. After 2.5 h the mixture was poured into H$_2$O (200 cm^3) and extracted with CH$_2$Cl$_2$ (3×80 cm^3). The combined organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% EtOAc–petrol) gave epoxide **22** (0.993 g, 89%) as a white solid; R_f 0.45 (50% EtOAc–petrol); mp 116–118 °C; ν_{max}/cm^{-1} 2980s, 2935m, 1705s, 1371s, 1299m, 1248m, 1211m, 1169s, 1112m, 1079m, 992m, 861m, 783w and 687m; δ_H (400 MHz, 2 rotamers observed) 4.43 and 4.28 (2H, two s, 3a,7a-H), 4.27 (2H, m, 4,7-H), 3.22 and 3.19 (2H, two d, *J*=3, 5,6-H),1.46 (12H, two s, OCMe$_3$ and MeCO$_2$) and 1.29 (3H, s, MeCO$_2$); δ_C (100 MHz) 157.2 (C=O), 113.0 (Me$_2$*C*O$_2$), 80.2 (O*C*Me$_3$), 80.0 and 79.3 (C3a, C7a), 60.9 and 60.3 (C5, C6), 48.0 and 47.4 (C4, C7), 28.2 (OC*Me*$_3$), 26.0 (Me), and 25.1 (Me); *m*/*z*[CI+(NH$_3$)] 284 (M+H$^+$, 10%), 245 (35), 184 (100), and 168 (20) (Found: M+H$^+$, 284.1496. $C_{14}H_{22}NO_5$ requires 284.1498).

4.2. Reaction of epoxide 22 with Bu^{n}Li

(a, Table 1, entry 4) Epoxide **22** (100 mg, 0.353 mmol) was added to a solution of Bu^{n}Li (1.5 mol dm^{-3} in hexanes; 0.80 cm^3, 1.24 mmol, 3.5 equiv.) and sparteine **2** (0.28 cm^3, 1.24 mmol, 3.5 equiv.) in Et$_2$O (3.5 cm^3) at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (14 h), and gave, following standard work-up and purification of the residue by column chromatography (50% EtOAc–petrol), four new compounds described below and recovered epoxide **22** (7 mg).

4.2.1. 1,1-Dimethylethyl (3aα,4β,5β,7aα)-[6-butyl-3a,4,5,7a-tetrahydro-5-hydroxy-2,2-dimethyl-1,3-benzodioxol-4-yl]carbamate 29. (19 mg, 16%) as a colourless liquid; R_f 0.50 (20% EtOAc–petrol), 0.75 (50% EtOAc–petrol); ν_{max}(neat)/cm^{-1} 3524w, 3448w, 2959m, 2931s,

2873w, 1715s, 1505s, 1368s, 1229m, 1167s, 1047s and 876m; δ_H (400 MHz) 5.61 (1H, d, J=9 Hz, NH), 5.40 (1H, m, =CH), 4.61 (1H, m, 7a-H), 4.25 (1H, m, 3a-H), 3.92–3.80 (2H, m, 4-H and 5-H), 2.82 (1H, d, J=11 Hz, OH), 2.20 (2H, t, J=8 Hz, =CCH_2), 1.47 (9H, s, $OCMe_3$), 1.52–1.34 (4H, m, 2×CH_2), 1.41 (3H, s, $MeCO_2$), 1.34 (3H, s, $MeCO_2$) and 0.91 (3H, t, J=7 Hz, Me); δ_C (100 MHz) 155.5 (C=O), 141.4 (=C), 121.3 (=CH), 110.1 (O_2CMe), 79.8 ($OCMe_3$), 76.0 (C3a), 73.7 (C7a), 68.5 (C5), 49.3 (C4), 34.1 (CH_2), 29.6 (CH_2), 28.4 ($OCMe_3$), 28.2 ($MeCO_2$), 26.5 ($MeCO_2$), 22.4 (CH_2) and 13.9 (CH_2Me); m/z [CI+(NH_3)] 342 ($M+H^+$, 55%), 284 (100), 245(20), 228 (61) and 224 (35) (Found: $M+H^+$, 342.2280. $C_{18}H_{32}NO_5$ requires 342.2280).

4.2.2. 1,1-Dimethylethyl [(1*R,2*S**)-3-butyl-2-hydroxy-5-oxo-3-cyclohexen-1-yl]carbamate 30.** (16 mg, 16%) as a colourless liquid; R_f 0.50 (50% EtOAc–petrol); $[\alpha]_D^{23}=-16$ (c 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3364br s, 2960s, 2932s, 2873m, 1674s, 1504m, 1367m, 1283m, 1250m, 1164s, 1061w and 1017w; δ_H (400 MHz) 5.90 (1H, s, =CH), 5.00 (1H, d, J=8 Hz, NH), 4.35 (1H, br s, C*H*OH), 4.20 (1H, m, C*H*NHBoc), 2.65–2.52 (2H, m, CH_2C=O), 2.38 (2H, t, J=7 Hz, =CCH_2), 1.62–1.26 (4H, m, CH_2CH_2), 1.46 (9H, s, $OCMe_3$) and 0.94 (3H, t, J=7 Hz, Me); δ_C (125 MHz) 196.8 (C=O), 165.0 (=C), 155.0 (CO_2), 126.2 (=CH), 80.0 ($OCMe_3$), 68.6 (CHOH), 50.2 (CHNH), 39.0 (CH_2C=O), 34.5 (=CCH_2), 29.0 (CH_2), 28.3 ($OCMe_3$), 22.3 (CH_2) and 13.7 (Me); m/z [CI+(NH_3)] 301 ($M+NH_4^+$, 18%), 284 ($M+H^+$, 42), 268 (30), 245 (100), 229 (70), 212 (35), 150 (40), 135 (60) and 79 (32).

4.2.3. 1,1-Dimethylethyl (3aα,4β,7β,7aα)-5-butyl-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4,7-imine-8-carboxylate 31. (7.5 mg, 7%) as a colourless oil; R_f 0.41 (20% EtOAc–petrol); ν_{max}(neat)/cm^{-1} 2959s, 2933s, 2874w, 1709s, 1624w, 1368s, 1300m, 1160s, 1102m, 1063s and 859w; δ_H (400 MHz, 2 rotamers observed) 5.82 and 5.75 (1H, two m, =CH), 4.62 and 4.55 (1H, two m, CHN), 4.48 and 4.36 (1H, two m, CHN), 4.27 (2H, dd, J=15, 5 Hz, 3a,7a-H), 2.20–2.05 (2H, m, =CCH_2), 1.47 (3H, s, $MeCO_2$), 1.45 (9H, s, Me_3CO), 1.29 (3H, s, $MeCO_2$), 1.50–1.25 (4H, m, CH_2CH_2), 1.29 (3H, s, $MeCO_2$) and 0.88 (3H, br t, J=7 Hz, Me); m/z [CI+(NH_3)] 324 ($M+H^+$, 55), 224 (100), 123 (35), 100 (28) and 90 (80) (Found: $M+H^+$, 324.2176. $C_{18}H_{30}NO_4$ requires 324.2175).

4.2.4. 1,1-Dimethylethyl (3-butyl-2-hydroxyphenyl)carbamate 32. (9 mg, 10%) as a colourless oil; R_f 0.54 (20% EtOAc–petrol); ν_{max}(neat)/cm^{-1} 3322br m, 2957s, 2930s, 2871w, 1683s, 1526s, 1480s, 1368m, 1283m, 1246m, 1159s, 1067m, 866w and 770w; δ_H (400 MHz) 8.2 (1H, br s, OH), 6.96 (1H, dd, J=7, 2 Hz, 4-H), 6.85 (1H, dd, J=8, 2 Hz, 6-H), 6.79 (1H, dd, J=8, 7 Hz, 5-H), 6.62 (1H, br s, NH), 2.67 (2H, t, J=8 Hz, CH_2), 1.64–1.56 (2H, m, CH_2), 1.54 (9H, s, $OCMe_3$), 1.38 (2H, sxt, J=7 Hz, CH_2) and 0.94 (3H, t, J=7 Hz, Me); δ_C (100 MHz) 155.3 (C=O), 146.1 (=COH), 132.8 (=CCH_2), 126.6 (C4), 125.3 (=CNH), 120.1 (C6), 119.6 (C5), 82.1 ($OCMe_3$), 32.1 (CH_2), 30.2 (CH_2), 28.2 ($OCMe_3$), 22.7 (CH_2) and 14.0 (CH_2); m/z (EI) 266 ($M+H^+$, 20%), 265 (M^+, 100), 238 (15) and 225 (22); m/z [CI+(NH_3)] 283 ($M+NH_4^+$, 48%), 266 ($M+H^+$, 100), 227 (75), 165 (37), 214 (100), 198 (95) and 170 (35) (Found: $M+H^+$, 266.1752. $C_{15}H_{24}NO_3$ requires 266.1756).

(b, Table 1, entry 6) Epoxide **22** (100 mg, 0.353 mmol) was added to a solution of Bu^{n}Li (1.4 mol dm^{-3} in hexanes; 0.90 cm^3, 1.24 mmol, 3.5 equiv.) and bisoxazoline **4** (0.36 g, 1.24 mmol, 3.5 equiv.) in Et_2O (3.5 cm^3) at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (14 h), and gave, following standard work-up and purification of the residue by column chromatography (50% EtOAc–petrol), aminophenol **32** (49 mg, 52%, 69% based on recovered epoxide **22**).

(c, Table 1, entry 8) Epoxide **22** (100 mg, 0.353 mmol) was added to a solution of Bu^{n}Li (1.5 mol dm^{-3} in hexanes; 0.80 cm^3, 1.24 mmol, 3.5 equiv.) and sparteine **2** (0.28 cm^3, 1.24 mmol, 3.5 equiv.) in toluene (3.5 cm^3) at −78 °C. After 5 h at 78 °C the reaction was quenched to give, following standard work-up and purification of the residue by column chromatography (50% EtOAc–petrol), amino alcohol **29** (49 mg, 41%, 64% based on recovered epoxide **22**). $[\alpha]_D^{23}=-9$ (c 1.0 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate derivative (see Supporting information) was determined to be 76% by chiral HPLC (OD column, 10% EtOH in heptane, 1.0 cm^3 min^{-1}, $t_R$mj, 10.5; $t_R$mn, 14.2).

4.2.5. 1,1-Dimethylethyl (1*R,2*R**,4*S**,5*S**)-8-aza-3-oxatricyclo[3.2.1.0^{2,4}]-6-octene-8-carboxylate 23.** Peracetic acid (38% w/v in acetic acid; 1.38 cm^3, 7.77 mmol) was added to a mixture of diene **38**[33] (1.0 g, 5.2 mmol), NaOAc (20 mg) and Na_2CO_3 (1.6 g) in CH_2Cl_2 (20 cm^3) at 0 °C. The reaction mixture was stirred for a total of 36 h, with further peracetic acid (1.38 cm^3) added over this period. CH_2Cl_2 (10 cm^3) and 1 M HCl (5 cm^3) were then added and the aqueous layer was extracted with CH_2Cl_2 (3×20 cm^3). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (10 cm^3) and brine, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (75% Et_2O–petrol) gave epoxide **23** (0.83 g, 77%) as a white solid; R_f 0.28 (50% Et_2O–petrol); mp 108–109 °C (from Et_2O) (Found: C, 63.1; H, 7.25; N, 6.5. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.25; N, 6.7%); ν_{max}(KBr)/cm^{-1} 1698s, 1380s, 1258s, 1172s, 1101s and 906m; δ_H (400 MHz) 6.56–6.51 (2H, m, HC=CH), 4.71 (1H, d, J=2.0 Hz, CH), 4.58 (1H, dd, J=2.0, 0.5 Hz, CH), 3.48 (2H, 2×d, J=3.5 Hz, 2×CH–O) and 1.47 (9H, s, Bu^t); δ_C (100 MHz) 156.1 (C=O), 138.2 and 138.0 (C=C), 80.1 (CMe_3), 61.0 and 60.7 (2×CH–O), 57.1 and 56.7 (2×CH) and 28.2 and 28.1 (3×Me); m/z (CI) 210 ($M+H^+$, 15%), 155 (12), 110 (15) and 80 (100) (Found: $M+H^+$, 210.1131. $C_{11}H_{16}NO_3$ requires 210.1130).

4.2.6. 1,1-Dimethylethyl [(1*R,2*S**)-2-hydroxy-3-(1-methylethyl)-3,5-cyclohexadien-1-yl]carbamate 39.** (a) Epoxide **23** (70 mg, 0.34 mmol) was added to a solution of Pr^{i}Li (1.4 mol dm^{-3} in petrol; 0.50 cm^3, 0.70 mmol) in Et_2O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and gave, following standard work-up and purification of the residue by column chromatography (gradient elution, 30–50% Et_2O–petrol) diene **39** (19 mg, 22%) as a clear colourless oil; R_f 0.40 (50% Et_2O–petrol); ν_{max}(film)/cm^{-1} 3430br m, 2965s, 1694s, 1499s, 1367s, and 1167s; δ_H (500 MHz) 6.01–5.97 (1H, m, *H*C=CH), 5.75 (1H, d, J=5.5 Hz, HC=C*H*), 5.56 (1H, dd, J=9.5,

2.0 Hz, C═CH), 5.23–5.21 (1H, m, NH), 4.45 (1H, s, C*H*NHBoc), 3.94 (1H, d, *J*=4.0 Hz, C*H*OH), 2.49 (1H, septet, *J*=7.0 Hz, CH of Pr^i), 1.68 (1H, br s, OH), 1.47 (9H, s, Bu^t), 1.12 (3H, d, *J*=7.0 Hz, Me) and 1.11 (3H, d, *J*=7.0 Hz, Me); δ_C (100 MHz) 155.9 (C═O), 147.5 (HC═*C*, quat.), 127.1 (H*C*═C), 124.7 (H*C*═CH), 117.5 (HC═*C*H), 79.6 (*C*Me$_3$), 67.8 (CHOH), 52.4 (CHNH), 32.4 (CH of Pr^i), 28.4 (3×Me), 22.0 (Me) and 21.3 (Me); *m*/*z* (CI) 196 (10%), 180 (15), 154 (M−Boc, 50) and 136 (M−NHBoc, 100) (Found: M+H$^+$, 254.1756. $C_{14}H_{24}NO_3$ requires 254.1756).

(b) Epoxide **23** (70 mg, 0.34 mmol) was added to a solution of Pr^{i}Li (1.4 mol dm^{-3} in petrol; 0.50 cm^3, 0.70 mmol) and (−)-sparteine **2** (0.16 cm^3, 0.70 mmol) in Et$_2$O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and gave, following standard work-up and purification of the residue by column chromatography (gradient elution, 30–0% Et$_2$O–petrol) gave diene **39** (27 mg, 32%) as a clear colourless oil; $[\alpha]_D^{24}$=−40.4 (*c* 1.0 in CHCl$_3$). The ee was determined to be 79% by chiral HPLC (AD Column, 10% EtOH in hexane, 0.4 cm^3 min^{-1}, t_R mj, 12.0; t_R mn, 15.5).

4.2.7. 1,1-Dimethylethyl (1a*R,2*R**,7*S**,7a*S**)-1a,2,7,7a-tetrahydronaphth[2,3-b]oxiren-2,7-imine-8-carboxylate 24.** Oxone (5.1 g, 8.3 mmol) and Na$_2$EDTA (16 mg, 0.04 mmol) in H$_2$O (21 cm^3) was added slowly (over 1 h) to a vigorously stirred mixture of alkene **40**[34] (200 mg, 0.82 mmol), NaHCO$_3$ (1.4 g, 17 mmol) and Bu$_4$NHSO$_3$ (56 mg, 0.19 mmol) in acetone (0.7 cm^3) and CH$_2$Cl$_2$ (10 cm^3). The pH was maintained at 7.8–8.0 by the addition of NaHCO$_3$. The reaction mixture was stirred vigorously for a total of 3 days with further addition of oxone (5 g, 8.1 mmol). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3×30 cm^3). The organic layers were combined, dried (MgSO$_4$) and evaporated under reduced pressure to yield a cream solid. Purification of the residue by column chromatography (gradient elution, 20–50% Et$_2$O–petrol) gave epoxide **24** (170 mg, 80%) as a white solid; R_f 0.47 (50% Et$_2$O–petrol); mp (Et$_2$O–petrol) 123.5–124.5 °C (Found: C, 69.5; H, 6.5; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); ν_{max}(KBr)/cm^{-1} 2977m, 1709s, 1371s, 1253s and 1169s; δ_H (400 MHz) 7.34–7.29 (2H, m, 2×CH of Ar), 7.18–7.13 (2H, m, 2×CH of Ar), 5.16 (1H, s, CH), 5.04 (1H, s, CH), 3.47 (1H, d, *J*=3.5 Hz, CH–O), 3.45 (1H, d, *J*=3.5 Hz, CH–O) and 1.50 (9H, s, Bu^t); δ_C (100 MHz) 156.6 (C═O), 144.0 and 143.5 (2×C of Ar, quat.), 126.9 and 126.8 (2×CH of Ar), 121.7 and 121.5 (2×CH of Ar), 80.3 (*C*Me$_3$), 62.3 and 61.4 (2×CH), 55.2 and 54.7 (2×CH–O) and 28.2 (3×Me); *m*/*z* (CI) 260 (M+H$^+$, 5%), 160 (M−Boc, 15) and 130 (100) (Found: M+H$^+$, 260.1289. $C_{15}H_{18}NO_3$ requires 260.1286).

4.2.8. Reaction of epoxide 24 with Pr^{i}Li. (a) Epoxide **24** (80 mg, 0.31 mmol) was added to a solution of Pr^{i}Li (1.4 mol dm^{-3} in petrol; 0.44 cm^3, 0.62 mmol) in Et$_2$O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and following standard work-up the residue by was purified by column chromatography (20% Et$_2$O–petrol).

First to elute was 1,1-dimethylethyl [3-(1-methylethyl)-naphthalen-2-yl]carbamate **42** (5 mg, 6%) isolated as a white solid; R_f 0.64 (50% Et$_2$O–petrol); mp 110–112 °C; ν_{max}(film)/cm^{-1} 3336br s, 2963m, 1696s, 1534s, 1367s and 1159s; δ_H (400 MHz) 7.85–7.80 (3H, m, 3×CH of Ar), 7.47–7.45 (3H, m, 3×CH of Ar), 6.85 (1H, br s, NH), 3.07 (1H, septet, *J*=7.0 Hz, CH of Pr^i), 1.58 (9H, s, Bu^t) and 1.36 (6H, d, *J*=7.0 Hz, 2×Me); δ_C (100 MHz) 153.4 (C═O), 146.6 (2×C of Ar, quat.), 134.2 (C of Ar, quat.), 132.8 (C of Ar, quat.), 128.4 (CH of Ar), 125.8 (CH of Ar), 125.2 (CH of Ar), 120.5 (CH of Ar), 120.2 (CH of Ar), 118.4 (CH of Ar), 80.5 (*C*Me$_3$), 34.3 (CH of Pr^i), 28.4 (3×Me of Boc) and 23.8 (2×Me); *m*/*z* (EI) 285 (M$^+$, 10%), 229 (M−CMe$_3$, 75), 185 (M−Boc, 40), 170 (50) and 57 (100) (Found: M$^+$, 285.1729. $C_{18}H_{23}NO_2$ requires 285.1729).

Second to elute was 1,1-dimethylethyl 1-(1-hydroxy-2-methylpropyl)-1*H*-isoquinoline-2-carboxylate **43** (16 mg, 17%) isolated as a clear colourless oil; R_f 0.55 (50% Et$_2$O–petrol); ν_{max}(film)/cm^{-1} 3483br w, 2975m, 1707s, 1629m, 1353s and 1166s; δ_H (400 MHz) (1:1 mixture of rotational isomers or diastereoisomers observed) 7.27–7.08 (4H, m, 4×CH of Ar), 7.01 and 6.85 (1H, 2×d, *J*=8.0, *H*C═CH), 5.92 and 5.79 (1H, 2×d, *J*=8.0 Hz, HC═C*H*), 5.39 and 5.17 (1H, 2×d, *J*=6.5 Hz, C(1)H), 3.52–3.49 (1H, m, C*H*OH), 1.73 (1H, septet, *J*=6.5 Hz, CH of Pr^i), 1.55 and 1.52 (9H, 2×s, Bu^t), 1.46–1.45 and 1.26–1.24 (1H, 2×m, OH), 1.06 (3H, d, *J*=7.0 Hz, Me) and 1.01 (3H, d, *J*=7.0 Hz, Me); δ_C (100 MHz) (4:3 mixture of rotational isomers or diastereoisomers observed) 152.3 and 152.0 (C═O), 131.7 and 131.4 (C of Ar, quat.), 128.9 and 128.6 (C of Ar, quat.), 128.3, 128.1, 127.9, 127.8 and 126.6 (3×CH of Ar), 126.4 and 126.3 (*C*═C), 124.8 and 124.6 (3×CH of Ar), 109.1 and 108.2 (C═*C*), 82.1 and 81.7 (*C*Me$_3$), 77.8 and 77.1 (CHOH), 57.4 and 56.5 (C2), 28.8 (CH of Pr^i), 28.4, 28.3 and 28.2 (3×Me), 20.6 (Me) and 16.6 and 16.4 (Me); *m*/*z* (EI) 303 (M$^+$, 80%) and 247 (M−CMe$_3$, 100) (Found: M$^+$, 303.1829. $C_{18}H_{25}NO_3$ requires 303.1834).

Third to elute was 1,1-dimethylethyl [(1*R**,2*S**)-1,2-dihydro-2-hydroxy-3-(1-methylethyl)naphthalen-1-yl]-carbamate **41** (30 mg, 32%) isolated as a clear colourless oil; R_f 0.45 (50% Et$_2$O–petrol); ν_{max}(film)/cm^{-1} 3432br w, 2965m, 1716s, 1498s, 1367m and 1170s; δ_H (400 MHz) 7.32–7.30 (1H, m, CH of Ar), 7.25–7.23 (2H, m, 2×CH of Ar), 7.11–7.09 (1H, m, CH of Ar), 6.30 (1H, br s, C═CH), 5.40–5.38 (1H, m, NH), 4.93–4.90 (1H, m, C*H*NHBoc), 4.08 (1H, d, *J*=4.0 Hz, C*H*OH), 2.59 (1H, septet, *J*=7.0 Hz, CH of Pr^i), 1.53 (9H, s, Bu^t), 1.21 (3H, d, *J*=7.0 Hz, Me) and 1.19 (3H, d, *J*=7.0 Hz, Me); δ_C (100 MHz) 156.3 (C═O), 147.4 (C of Ar, quat.), 133.0 (C of Ar, quat.), 132.8 (CH═*C*, quat.), 127.7 (CH of Ar), 127.6 (CH of Ar), 126.7 (CH of Ar), 125.7 (H*C*═C), 122.1 (CH of Ar), 79.7 (*C*Me$_3$), 68.7 (CHOH), 54.0 (*C*HNHBoc), 32.8 (CH of Pr^i), 28.4 (3×Me), 21.8 (Me) and 21.5 (Me); *m*/*z* (EI) 303 (M$^+$, 30%), 285 (35) and 247 (M−CMe$_3$, 100) (Found: M$^+$, 303.1835. $C_{18}H_{25}NO_3$ requires 303.1834).

(b) Epoxide **24** (70 mg, 0.27 mmol) was added to a solution of Pr^{i}Li (1.0 mol dm^{-3} in petrol; 0.81 cm^3, 0.81 mmol) and TMEDA (0.13 cm^3, 0.86 mmol) in Et$_2$O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and gave, following standard work-up and purification of the residue by column chromatography (20% Et$_2$O–petrol) naphthylamine **42** (50 mg, 65%).

(c) Epoxide **24** (80 mg, 0.31 mmol) was added to a solution of Pr^{i}Li (1.0 mol dm^{-3} in petrol; 0.62 cm^3, 0.62 mmol) and (−)-sparteine **2** (0.15 cm^3, 0.65 mmol) in Et_2O at −78 °C. After 5 h at −78 °C the reaction was warmed to 0 °C (1 h), and following standard work-up the residue by was purified by column chromatography (20% Et_2O–petrol).

First to elute was naphthylamine **42** (12 mg, 14%). Second to elute was 1,1-dimethylethyl 1-formyl-1*H*-isoquinoline-2-carboxylate **44** (26 mg, 33%) isolated as a clear colourless oil; R_f 0.55 (50% Et_2O–petrol); ν_{max}(film)/cm^{-1} 3397br s, 2978m, 1715s, 1630m, 1369s and 1160s; δ_H (400 MHz) (2:1 mixture of rotational isomers observed) 9.46 and 9.42 (1H, 2×s, H–C═O), 7.31–7.22 (3H, m, 3×CH of Ar), 7.13 and 6.97 (1H, 2×d, J=8.0 Hz, *H*C═CH), 7.06 (1H, d, J=7.0 Hz, CH of Ar), 5.79 and 5.59 (1H, 2×s, C(1)H), 5.71 and 5.65 (1H, 2×d, J=8.0 Hz, HC═C*H*), and 1.55 and 1.52 (9H, 2×s, Bu^t); δ_C (100 MHz) (2:1 mixture of rotational isomers observed) 194.7 and 194.4 (C═O of aldehyde), 151.9 (C═O), 131.3 (C of Ar, quat.), 129.2 and 129.0 (CH of Ar), 127.4 and 127.3 (C═*C*), 127.1 and 126.9 (CH of Ar), 126.2 and 126.0 (CH of Ar), 125.2 and 125.0 (CH of Ar), 124.0 (C of Ar, quat.), 106.1 (*C*═C), 82.6 and 82.5 (*C*Me$_3$), 65.6 and 64.4 (CHOH) and 28.4, 28.1 and 28.0 (3×Me); *m/z* (CI) 188 (M−OMe$_3$, 5%), 158 (M−Boc, 5) and 130 [M−(Boc, formyl), 100] (too unstable for accurate mass measurement).

Third to elute was amino alcohol **41** (28 mg, 30%); $[\alpha]_D^{23}$=−45.2 (*c* 1.0 in $CHCl_3$). The ee was determined to be 71% by chiral HPLC (OD Column, 10% EtOH in hexane, 0.25 cm^3 min^{-1}, t_R mj, 19.0; t_R mn, 35.0).

4.3. Supporting information

Electronic supporting information available: determination of the absolute configuration of (−)-**16** and the preparation and characterisation of representative derivatives for ee determinations.

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