Stereoselective solvent induced 1,3-proton transfer of an allylic alkoxide to a homoallylic alkoxide catalysed by a chiral lithium amide †

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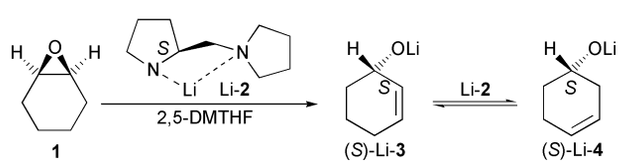
Stereoselective rearrangements of *e.g. meso*-epoxides by chiral lithium amides yield chiral allylic alcohols in high enantiomeric excess. Such products are useful synthetic intermediates. Lithium (*S*)-2-(pyrrolidin-1-ylmethyl)-pyrrolidide Li-**2** has been found to deprotonate cyclohexene oxide **1** in tetrahydrofuran (THF) to yield the allylic lithium alkoxide of (*S*)-cyclohex-2-en-1-ol (*S*)-Li-**3** in 80% ee. Upon changing solvent from THF to 2,5-dimethyltetrahydrofuran (2,5-DMTHF) a 1,3-proton transfer of (*S*)-Li-**3** is induced yielding the lithium alkoxide of (*S*)-cyclohex-3-en-1-ol (*S*)-Li-**4**. Thus the reaction gives access to the homoallylic alcohol **4**. This rearrangement has previously been shown to take place with retention of the stereocenter and intramolecularly. We here report further results on the stereochemistry of this isomerisation. For this purpose a synthesis of the deuterium labelled compound, (*S*)-2-deuterio-3-methylcyclohex-2-en-1-ol (*S*)-^{2}H-**5**, has been developed. Solvent induced isomerisation of the lithium alkoxide of (*S*)-^{2}H-**5** in 2,5-DMTHF gave after isolation only the rearrangement product (1*S*,2*R*)-2-deuterio-3-methylcyclohex-3-en-1-ol (1*S*,2*R*)-^{2}H-**6** as shown by NMR and computational modelling. No trace of the isotopomer and diastereoisomer (1*S*,2*S*)-^{2}H-**6** could be detected. Thus it is concluded that the rearrangement stereoselectively protonates the C-2 carbon *anti* to the alkoxide oxygen to yield the product. Further details of the reaction mechanism are currently under investigation.

Introduction

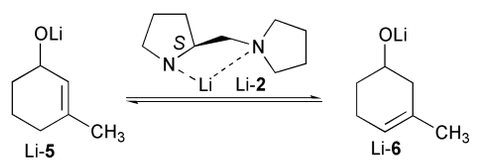
Lithium organic compounds are among the most useful reagents in synthesis. But surprisingly little is known about their reaction mechanisms. To explore the full potential of this chemistry detailed knowledge about the reaction mechanisms is needed including the stereochemistry and the role of aggregation and the solvent in the reactions.

Chiral lithium amides for enantioselective deprotonation of *e.g. meso*-epoxides into allylic alcohols in high enantiomeric excess (ee) are being developed and used.[1–3] For example, the lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide Li-**2** deprotonates cyclohexene oxide **1** in tetrahydrofuran (THF) to (*S*)-cyclohex-2-en-1-ol (*S*)-**3** in 80% ee.[4–7] It has previously been shown that upon changing the solvent from THF to a more sterically demanding solvent, *e.g.* 2,5-dimethyltetrahydrofuran (2,5-DMTHF) or diethyl ether (DEE), isomerisation of the allylic lithium alkoxide (*S*)-Li-**3** to the homoallylic lithium alkoxide of (*S*)-cyclohex-3-en-1-ol (*S*)-Li-**4** is induced (Scheme 1).[8] This observation suggests that such reactions might find general use for preparation of chiral homoallylic alcohols which are important starting materials for making other optically active compounds. A number of drugs, pheromones and other biologically active compounds may be synthesized using this type of building block.[9–12]

In our previous mechanistic studies of the isomerisation[13] the substrate seudenol (a sex pheromone of the Douglas fire beetle), 3-methylcyclohex-2-en-1-ol **5**, has been used. The methyl group at the double bond effectively prevents the homoallylic lithium alkoxide Li-**6** from further rearrangements (Scheme 2).



Scheme 1 Enantioselective deprotonation of the epoxide **1** by the lithium amide Li-**2** in 2,5-DMTHF and subsequent solvent induced isomerisation of the allylic alkoxide (*S*)-Li-**3** into the homoallylic alkoxide (*S*)-Li-**4**.



Scheme 2 Isomerisation of the allylic lithium alkoxide Li-**5** into the homoallylic alkoxide Li-**6** by the lithium amide Li-**2**.

With this substrate it was shown that the solvent induced isomerisation is 100% stereospecific *i.e.* the configuration at the stereogenic carbon center is conserved during the rearrangement. The 1,3-proton transfer was also shown to be close to 100% intramolecular.[13]

We now wish to report on the stereoselectivity of the solvent induced chiral lithium amide catalysed 1,3-proton transfer reaction. There are four possible modes for this isomerisation. It may take place *suprafacially* either on the side of the ring *syn* to the oxygen or the ring-side *anti* to the oxygen. If on the other hand the 1,3-proton transfer takes place *antarafacially* the proton may be abstracted by the base from one or the other side

† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{1}H,^{1}H-COSY NMR and ^{1}H,^{1}H-NOESY NMR spectra of **6**; ^{1}H NMR spectra of **5** and (*S*)-^{2}H-**5**; ^{2}H NMR spectrum of (*S*)-^{2}H-**5**. See http://www.rsc.org/suppdata/p2/b1/b111676b/

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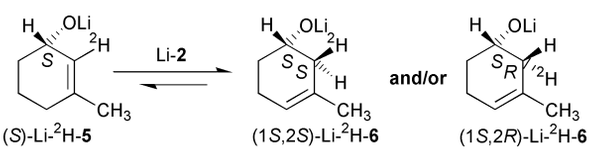
of the ring and delivered to the opposite side of the ring *syn* or *anti* to the oxygen, respectively. Results are presented on the determination of the absolute stereochemistry of the isolated rearrangement product, the homoallylic alcohol. For this purpose a deuterium labelled seudenol has been designed and synthesised and used in the isomerisation reaction. Using two-dimensional NMR-investigations and computational chemistry it is concluded that the abstracted proton from the lithium alkoxide of deuterated seudenol is delivered to the 2-carbon *anti* with respect to the oxygen to yield only one of the stereo-isomers of the deuterium labelled homoallylic alcohols after isolation.

Results and discussion

Below the design, synthesis and application of mono-deuterium labelled seudenol are presented together with results from the NMR-studies and computational studies.

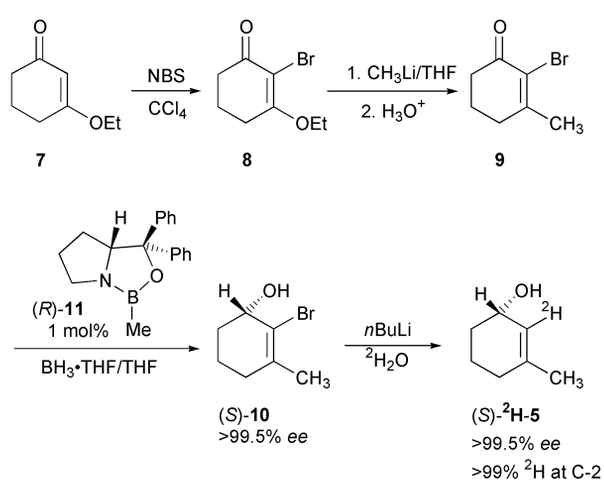
Design and synthesis of a deuterium labelled substrate

For the determination of the product stereochemistry of the reaction, *i.e.* to answer the question whether the 1,3-proton transfer has delivered the proton to the C-2 carbon *syn* or *anti* to the oxygen on the ring, the deuterium labelled substrate, (*S*)-2-deuterio-3-methylcyclohex-2-en-1-ol (*S*)-^{2}H-**5**, was designed and synthesised. It was predicted that after isomerisation of (*S*)-Li-^{2}H-**5** by Li-**2** into lithium (1*S*,2*X*)-2-deuterio-3-methylcyclohex-3-en-1-ol (1*S*,2*X*)-Li-^{2}H-**6** (*X* = *R* or *S*), *X* could be determined by NMR (Scheme 3).



Scheme 3 Isomerisation of (*S*)-Li-^{2}H-**5** by Li-**2** yielding (1*S*,2*S*)-Li-^{2}H-**6** and/or (1*S*,2*R*)-Li-^{2}H-**6**.

The labelled seudenol (*S*)-^{2}H-**5** was synthesized from commercially available 3-ethoxycyclohex-2-enone **7** following the procedure shown in Scheme 4.



Scheme 4 Synthetic procedure used for preparation of (*S*)-^{2}H-**5**.

In the first step the ketone **7** was brominated in the dark by *N*-bromosuccinimide (NBS) and 2-bromo-3-ethoxycyclohex-2-enone **8** was obtained following a procedure by Belmont and Paquette.[14,15] In the next step the bromoketone **8** was reacted with methyllithium in THF, following a published procedure[14,15] and 2-bromo-3-methylcyclohex-2-enone **9** was obtained in up to 73% crude yield from **7**.

To obtain the chiral bromoalcohol (*S*)-2-bromo-3-methylcyclohex-2-en-1-ol (*S*)-**10** a method by Corey and co-workers for enantioselective reduction of unsymmetrical ketones was employed.[16,17] The chiral oxazaborolidine (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]-oxazaborole[18] (*R*)-**11** was used together with BH_3•THF and the product contained (*S*)-**10** in 80–86% ee as determined by chiral gas chromatography (GC). The crude product was purified by flash column chromatography. Typically, the overall yield from starting material was 45%. After repeated recrystallisations (typically 3 times) from hexane pure **10** containing (*S*)-**10** in >99.5% ee was obtained.

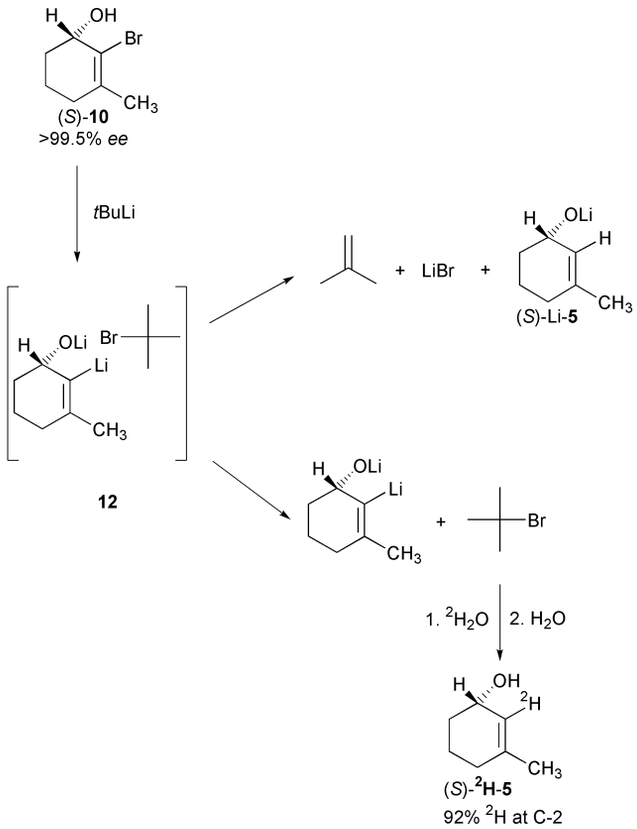
To introduce the deuterium and obtain the final product a procedure by Wu and Okamura[19] was tried in which *tert*-butyllithium (*t*BuLi) in DEE is used for lithium–bromine exchange of (*S*)-**10** followed by quenching with ^2H_2O. Using this method (*S*)-2-deuterio-3-methylcyclohex-2-en-1-ol (*S*)-^{2}H-**5** was obtained, but the deuterium content was only 92 atom% at C-2 as determined by ^{1}H-NMR. Deuterium was only found to be introduced at C-2 as determined by 1D ^{2}H-NMR.

In order to increase the deuterium content several modifications were made to the above procedure. In the Wu and Okamura procedure the *t*BuLi is used in 4.2 times molar excess over alcohol and added dropwise at −78 °C to the vinyl bromide dissolved in diethyl ether. A reverse procedure with the vinyl bromide dissolved in diethyl ether and addition to the *t*BuLi solution was tried, but the deuterium content of the final product remained unchanged. A larger excess (42 times molar excess over alcohol) of *t*BuLi was also used but under these conditions the deuterium content at C-2 in the product dropped to 80 atom%. In order to reach improvement the hydroxylic protons in the starting alcohol were exchanged by deutrons by exchange with ^2H_2O or $C^2H_3O^2H$, prior to reaction with *t*BuLi. However, the deuterium content of the isolated product remained essentially unchanged. The quenching procedure was also modified *e.g.* the reaction was quenched by $C^2H_3O^2H$ at −78 °C, but the deuterium content of the product did not increase significantly. These results suggest that the protium contamination of the product could be due to the fact that *tert*-butyl bromide, formed from *t*BuLi in the lithium–bromine exchange, partially undergoes a β-elimination by reaction with vinyllithium in a reaction intermediate **12** (Scheme 5).

Therefore an alkyllithium reagent yielding in the halogen–lithium exchange a bromide that undergoes no or slower elimination was employed. However, no lithium–bromine exchange was detected with methyllithium. But when *t*BuLi was exchanged for *n*BuLi, which would give a much less stabilized alkene, and therefore a presumably much slower elimination, (*S*)-^{2}H-**5** with a deuterium content of >99 atom% at C-2 was obtained. The ee of (*S*)-^{2}H-**5** was >99.5% and the crude yield was up to 99%. This product was used as a substrate in the 1,3-proton transfer reactions presented below for determination of the stereochemistry.

Interpretation of the ^{1}H NMR spectrum of 6

Assignment of the NMR signals to the carbons and hydrogens in **6** was made by heteronuclear two-dimensional shift correlation NMR—the heteronuclear single quantum correlation experiment (^{1}H,^{13}C-HSQC) and the proton–proton correlation experiment (^{1}H,^{1}H-COSY). To be able to differentiate the two hydrogens at C-2 in **6** a homonuclear two-dimensional ^{1}H,^{1}H-NOESY experiment was performed and NOEs between the protium at C-1 and the protiums at C-2 were determined, as well as NOEs between the protiums at C-2 and C-6. A much stronger NOE was found between the protium at C-2 with the chemical shift 2.26 ppm and the protium at C-1 with the chemical shift 3.98 ppm, than between the other protium at C-2 with the chemical shift 1.95 ppm and the protium at C-1. A weak NOE was also found between the protium at C-2 with the chemical shift 1.95 ppm and the protium at C-6 with the chemical shift 1.57 ppm. No NOE was observed between the protiums at



Scheme 5 A mechanism for the formation of the deuterated product is shown together with a possible route to proton contaminated product when using *t*BuLi.

1.95 and 2.26 ppm and the protium at 1.81 ppm. The vicinal coupling constants between the protium at C-1 with the chemical shift 3.98 ppm and the protiums at C-2 with the chemical shifts 1.95 and 2.26 ppm were found to be 6.4 and 3.5 Hz, respectively.

In the conformer with the hydroxy group in the equatorial position (Fig. 1) NOE between the protiums H-2*anti* and H-1 is

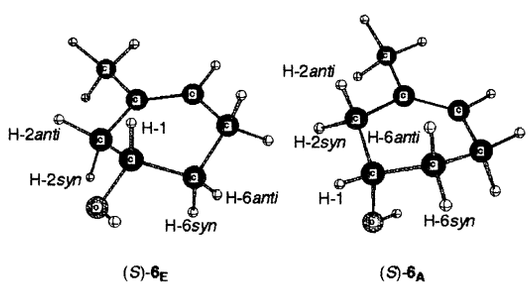


Fig. 1 Geometry optimized (B3LYP/6-31+G(d)) structures of conformers of (*S*)-**6** with the hydroxy group in an equatorial position ((*S*)-$\mathbf{6}_{E}$) and an axial position ((*S*)-$\mathbf{6}_{A}$).

predicted, but a negligible one between H-2*syn* and H-1. A weak NOE is also expected between H-2*syn* and H-6*syn*. In addition one would expect to find a large vicinal coupling constant between H-1 and H-2*syn* and a smaller one between H-1 and H-2*anti*.

On the other hand for the conformer with the hydroxy group in an axial position (Fig. 1) large NOEs are predicted between H-1 and H-2*syn* as well as H-2*anti* and a weak one between H-2*anti* and H-6*anti*. Moreover for this conformer the vicinal coupling constants between H-1 and H-2*syn* and H-2*anti* are predicted to be similar.

Thus our results suggest that the protium at C-2 with the chemical shift 2.26 ppm is on the same side of the ring as the protium at C-1. They also suggest that the conformer with the hydroxy group in the equatorial position is the main conformer, so that the protium at C-2 with the chemical shift 1.95 ppm and the protium at C-6 with the chemical shift 1.57 ppm are in proximity. The explanation for the observed NOE between the protium with the chemical shift 1.95 ppm (H-2*syn*) and the proton at 3.98 ppm (H-1) is that conformers with the hydroxy group in an axial position are also present. This assignment is in agreement with other examples showing that the axial hydrogens at positions C-2 and C-6 have lower chemical shifts than the equatorial ones.

A detailed interpretation of the results has been performed using predictions of the coupling constants, based on DFT calculations (B3LYP/6-31+G(d)). The calculations show that the conformer with an equatorial hydroxy group is more stable by 0.74 kcal mol^{-1}. Thus these gas-phase calculations predict that 78% of the conformers have their hydroxy groups in equatorial positions at 298 K.

The vicinal coupling constants for the two different conformers have been calculated using the Karplus equation:[20]

$$^{3}J = A + B\cos\varphi + C\cos 2\varphi \qquad (1)$$

where ^{3}J is the vicinal coupling constant, φ is the dihedral angle and A, B and C are constants given the values 4.22, −0.5, and 4.5 respectively.[20] Using the dihedral angles, obtained from the DFT calculations, the vicinal coupling constants in (*S*)-$\mathbf{6}_{E}$ (Fig. 2) were calculated to be 8.5 Hz between H-1 and H-2*syn* and 3.3 Hz between H-1 and H-2*anti*, respectively. The vicinal coupling constants in (*S*)-$\mathbf{6}_{A}$ (Fig. 2) were calculated to be 0.7 Hz between H-1 and H-2*syn* and 3.72 Hz for the coupling between H-1 and H-2*anti*, respectively. The weighted averages of the vicinal coupling constants, *i.e.* assuming a 78 : 22 distribution between the conformers as suggested by the calculations, were calculated to be 6.8 Hz (6.4 Hz) between H-1 and H-2*syn* and 3.4 Hz (3.5 Hz) for the coupling between H-1 and H-2*anti*. The experimentally observed values are shown in parentheses. If the influence of the electronegativity of substituents is also taken into account slightly lower vicinal coupling constants are predicted.

The result of the interpretation is shown in Fig. 2.

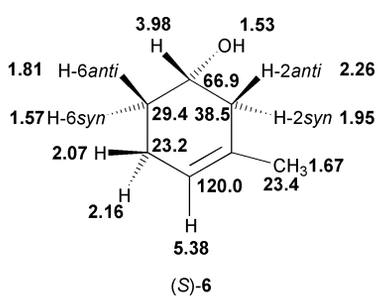


Fig. 2 Assigned NMR chemical shifts to the carbons and hydrogens in **6** based on $^{1}H,^{13}C$-HSQC and $^{1}H,^{1}H$-COSY NMR experiments and DFT calculations.

The stereochemistry of the isomerisation product

The determination of the configuration at C-2 in the isomerisation product is based upon the chemical shift assignments of the protons at C-2 in **6**. The pure enantiomer (*S*)-^{2}H-**5** from the synthesis described above was used in the 1,3-proton transfer reaction with the chiral lithium amide Li-**2** to determine whether the proton is delivered to the C-2 carbon *syn* or *anti* to the oxygen (Scheme 3). After 240 h reaction the mixture of starting material and product was purified by flash chromatography giving a 35 : 65 mixture of (*S*)-^{2}H-**5** and (1*S*,2*X*)-^{2}H-**6**. The isolated yield was 83%. The alcohols were separated by HPLC and analyzed by ^{1}H- and ^{2}H-NMR. All deuterium was found at C-2 in (*S*)-^{2}H-**5** and (1*S*,2*X*)-^{2}H-**6**, respectively. Only one deuterium signal at 1.95 ppm was detected for the

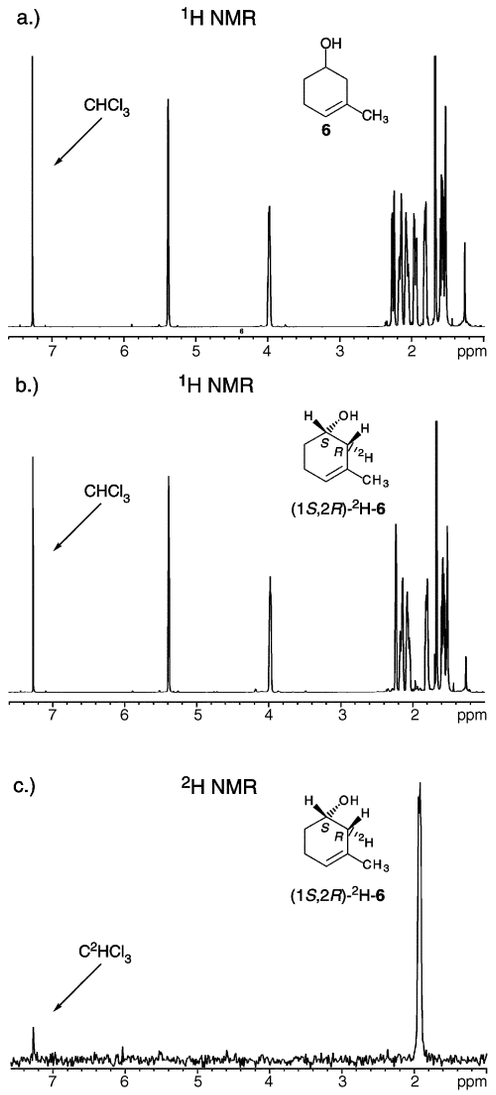


Fig. 3 a) ^{1}H NMR spectrum of **6** recorded at 600 MHz and 25 °C (72 mM in C^{2}HCl$_3$). b) ^{1}H NMR spectrum of (1*S*,2*R*)-^{2}H-**6** recorded at 600 MHz and 25 °C (66 mM in C^{2}HCl$_3$). c) ^{2}H NMR spectrum of (1*S*,2*R*)-^{2}H-**6** recorded at 92 MHz and 25 °C (95 mM in CHCl$_3$).

isolated homoallylic alcohol *i.e.* no trace of deuterium in the 2*anti* position was detected (Fig. 3).

Thus it is concluded that deuterium is *syn* to the oxygen in the deuterium labelled homoallylic alcohol product *i.e.* the 1,3-proton transfer has delivered the proton *anti* with respect to the oxygen as shown in Fig. 4 *i.e.* selectively to yield the

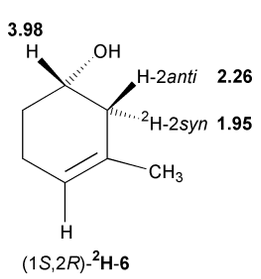


Fig. 4 The stereochemistry of the rearranged product is shown. The rearranged proton is found at C-2 in a position *anti* with respect to the oxygen.

enantiomer (1*S*,2*R*)-^{2}H-**6** as the product. No trace of the stereoisomer (1*S*,2*S*)-^{2}H-**6** could be detected. It is not yet clear whether a monomer or a dimer of the lithium amide (Li-**2**) is carrying out the 1,3-proton transfer and whether the rearrangement is *suprafacial* or *antarafacial*; experiments to address this question are currently underway.

Experimental

Synthesis of 2-bromo-3-ethoxycyclohex-2-enone 8

A procedure by Belmont and Paquette was followed with the following modification.[14,15] Crystals of recrystallised NBS were added very slowly in portions (up to 2.5 hours). The bromoketone **8** was obtained in up to 99% yield.

Synthesis of 2-bromo-3-methylcyclohex-2-enone 9

A procedure by Belmont and Paquette was followed.[14,15] The crude **9** was obtained in up to 74% yield and used in the next step without further purification.

Synthesis of (*S*)-2-bromo-3-methylcyclohex-2-en-1-ol (*S*)-10

To the catalyst (*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (*R*)-**11** (185 µl, 0.28 mmol) was added BH_3·THF (2.77 ml, 1.0 M) with stirring under N_2. A solution of **9** (5.23 g, 27.7 mmol) in THF (10 ml) and a solution of BH_3·THF (13.8 ml, 13.8 mmol, 1.0 M) were added dropwise simultaneously to the catalyst solution with stirring at 30 °C under N_2 (addition rate 0.5 ml min^{-1}). The mixture was stirred for 3 hours at 30 °C and quenched by the addition of methanol (8 ml) at 0 °C. To the resulting solution was added HCl (15 ml, 2 M) and water (15 ml). The mixture was extracted with diethyl ether (3 × 75 ml). The combined ether phases were washed with brine (50 ml), saturated aqueous sodium bicarbonate solution (50 ml), brine (50 ml), and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave crude (*S*)-**10** as a yellow oil. The yield of product was up to 5.24 g (99%). ^{1}H NMR (400 MHz, C^{2}HCl$_3$): δ 4.27 (m, 1 H), 2.13 (m, 2 H), 1.88 (m, 2 H), 1.85 (s, 3 H), 1.79 (m, 1 H), 1.64 (m, 1 H). The ee of the crude product was 80% as determined by GC analysis. The product was purified by flash column chromatography (TLC silica gel 60H, eluent gradient hexane–DEE), giving white crystals of (*S*)-**10** after evaporation of solvent. Typical yield after chromatography was 2.4 g (45%). The ee of (*S*)-**10** was improved by repeated recrystallisations from hexane. The final ee was >99.5% of (*S*)-**10**.

Synthesis of (*S*)-2-deuterio-3-methylcyclohex-2-en-1-ol (*S*)-^{2}H-5

*n*BuLi (11 ml, 22 mmol, 2.0 M) was added dropwise to a solution of (*S*)-**10** (1.0 g, 5.2 mmol) in dry DEE (100 ml) with stirring at −78 °C under N_2. The reaction mixture was stirred for 1 hour at −78 °C and for 1 hour at 0 °C. ^2H_2O (2.5 ml) was added at 0 °C and the mixture was allowed to stir for 30 min at rt. Water (40 ml) was added and the mixture was extracted with diethyl ether (3 × 100 ml). The combined ether phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was obtained as a yellow oil in yields up to 0.58 g (>99%) and used in the isomerisation without further purification. ^{1}H NMR (600 MHz, C^{2}HCl$_3$): δ 4.18 (m, 1 H), 1.95 (m, 1 H), 1.88 (m, 1 H), 1.79 (m, 1 H), 1.75 (m, 1 H), 1.70 (s, 3 H), 1.57–1.60 (m, 2 H), 1.38 (m, 1 H). The deuterium content in the product was analyzed by ^{1}H- and ^{2}H-NMR and was found to be >99 atom% in position 2. The ee was >99.5%.

Isomerisation

Glassware and syringes used in the isomerisation reaction were dried at 50 °C in a vacuum oven overnight. 2,5-DMTHF was distilled from sodium–benzophenone ketyl in a nitrogen atmosphere before use. All manipulations concerning the isomerisation reactions were carried out in a glove box (Mecaplex GB 80 equipped with a gas purification system that removes oxygen and moisture) using gas-tight syringes.

Racemic 3-methylcyclohex-3-en-1-ol 6

Isomerisation of racemic Li-**5** into racemic Li-**6** was performed on up to a gram scale according to the following general

protocol for isomerisations: *n*BuLi (227 μl, 0.34 mmol, 1.5 M in hexane) was added to a solution of **5** (20.0 μl; 0.17 mmol) and **2** (28.0 μl; 0.17 mmol) in 2,5-DMTHF (1.00 ml) maintained at 0 °C. The flask was then moved to a thermostat held at 30.0 ± 0.02 °C. The reaction was monitored by withdrawing 50.0 μl of the reaction mixture using a dry syringe. The sample was transferred to a vial containing diethyl ether (1.0 ml) and saturated NH_4Cl (0.50 ml), and the mixture was shaken. The aqueous layer was removed and the ether phase was dried over Na_2SO_4 prior to GC analysis. After 72 h the reaction mixture contained **5** and **6** in about 35 : 65 ratio. Typical yield was 90%. For workup the organic layer was washed with a solution of NH_4Cl (1 M) followed by brine, prior to drying (Na_2SO_4) and evaporation of the solvent. The alcohol mixture was purified by silica gel flash chromatography (eluent 75 : 25 hexane–DEE) giving a pure mixture of **5** and **6** in 45% yield as shown by ^{1}H NMR and GC. The isomers were separated on an analytical and semi-preparative scale using HPLC (Dynamax silica column, solvent: 75 : 25 cyclohexane–EtOAc (analytical 1.2 ml min^{-1}, semipreparative 5.5 ml min^{-1})) with refractive index detection. ^{1}H NMR (600 MHz, C^{2}HCl$_3$): δ 5.38 (br, 1 H), 3.98 (m, 1 H), 2.26 (m, 1 H), 2.16 (m, 1 H), 2.07 (m, 1 H), 1.95 (m, 1 H), 1.81 (m, 1 H), 1.67 (s, 3 H), 1.57 (m, 2 H), 1.53 (br s, 1 H); ^{13}C{^{1}H} NMR (100 MHz, C^{2}HCl$_3$): δ 23.2, 23.4, 29.4, 38.5, 66.9, 120.0, 131.0.

Isomerisation of the lithium alkoxide of (*S*)-2-deuterio-3-methylcyclohex-2-en-1-ol Li-(*S*)-^{2}H-5 to the lithium alkoxide of (1*S*,2*R*)-2-deuterio-3-methylcyclohex-3-en-1-ol (1*S*,2*R*)-Li-^{2}H-6

(*S*)-2-(Pyrrolidin-1-ylmethyl)pyrrolidine **2** (474 μl, 2.91 mmol) and (*S*)-2-deuterio-3-methylcyclohex-2-en-1-ol (*S*)-^{2}H-**5** (0.47 g, 4.15 mmol) were dissolved in 2,5-DMTHF (13.95 ml) in the reaction vessel inside the glove box. The vessel was transferred out of the glove box and *n*BuLi (2.08 ml, 5.0 mmol, 2.4 M in hexane) was added under N_2. The vessel was transferred from the glove box to a thermostat (Heto Birkeröd) held at 30 ± 0.02 °C. After 240 h the reaction was quenched by addition of a saturated solution of NH_4Cl in water (10 ml). The organic layer was washed with brine (2 × 5 ml) before drying over Na_2SO_4 and evaporation of the solvent. The residue was purified by flash chromatography (silica gel TLC 60H, eluent 75 : 25 hexane : DEE) giving a 35 : 65 mixture of (*S*)-^{2}H-**5** and (1*S*,2*R*)-^{2}H-**6** in 83% yield (0.39 g). The mixture was separated by HPLC-separation following the procedure cited above, giving 0.22 g of (1*S*,2*R*)-^{2}H-**6**.

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