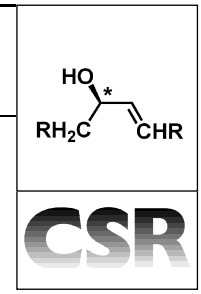
Asymmetric base-mediated epoxide isomerisation



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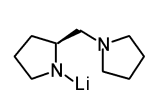
The base-mediated rearrangement of epoxides into allylic alcohols is a well-known synthetic transformation. The first enantioselective version of the reaction using a chiral base was reported in 1980. Since then, the reaction has received a lot of attention mostly due to the great usefulness of chiral allylic alcohols in organic synthesis. Major breakthroughs in the area were the first report on using a sub-stoichiometric amount of chiral base, and the development of chiral bases for a true catalytic reaction protocol. The present review covers the time from when the first asymmetric epoxide isomerisation reaction was reported (1980) up to now, focusing on the period 1997–2001.

Introduction

Allylic alcohols are versatile intermediates in organic synthesis, but multistep sequences are often required for their preparation. The lithium amide-mediated rearrangement of epoxides into allylic alcohols are an attractive approach which has been thoroughly investigated due to its synthetic potential and interesting mechanistic features. The first enantioselective β-deprotonation reaction of epoxides to produce enantio-enriched allylic alcohols was presented in 1980 by J. K. Whitesell and S. W. Felman.[1] Even though the enantioselectivity was low in this initial attempt, it opened up the way for further research in the area. The findings up to 1996 have been reviewed earlier[2–5] and include many of the to date commonly used chiral lithium amide bases (**1**–**4**). However, from the literature the low generality of



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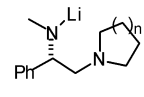

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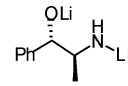

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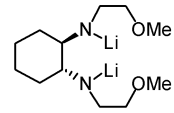

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the reaction and the need for superstoichiometric amounts of chiral base in order to induce acceptable enantioselectivities is clear . This review describes the development of the epoxide isomerization reaction from 1997 up to 2001. It is evident that

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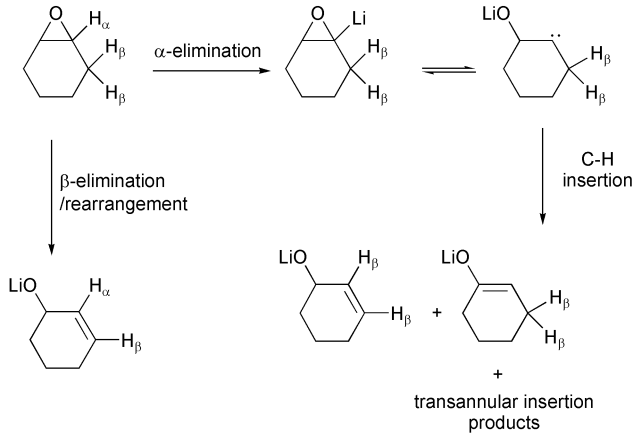
Pher G. Andersson

the scope of the reaction has increased markedly during the last few years, both due to the increased number of investigated substrates and reaction protocol improvements. Maybe the most important finding has been the development of catalytic versions of the reaction and it can now be considered as a valuable complement to the rather few other straightforward methods for the preparation of enantio-enriched allylic alcohols.[6–8]

Mechanism

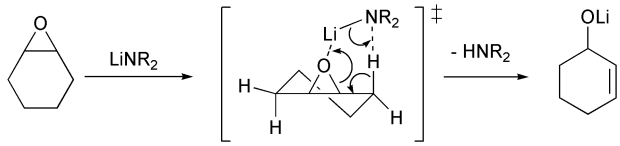
Epoxides can react with strong, non-nucleophilic bases, such as lithium amides, by deprotonation in either α- or β-position (illustrated by the deprotonation of cyclohexene oxide in Scheme 1).[9] Abstraction of the α-hydrogen gives rise to a



Scheme 1

reactive carbene intermediate, which undergoes C–H insertion to produce allylic alkoxide, enolate, and/or other insertion products. To control the regioselectivity in the insertion step is difficult which limits the synthetic scope of the α-lithiation. The β-deprotonation pathway on the other hand, is accompanied by a stereospecific rearrangement which leads to exclusive formation of allylic alkoxides (Scheme 1). The relative rates of α- and β-deprotonation are primarily substrate dependent, but in some cases the choice of base and reaction conditions can affect the regioselectivity in the reaction.

The β-elimination is thought to occur *via* a *syn*-elimination reaction pathway. For cyclic epoxides, this implies abstraction of a proton in a pseudo-axial orientation (Scheme 2). The *syn*-elimination, which is unfavored in many other E_2-type reactions, is assumed to be accelerated by complexation of the lithium ion of the base with the epoxide oxygen (Scheme 2).



Scheme 2

Enantiodiscrimination

The only selectivity model in the literature up to 1997 describes the enantioselectivity observed when using the proline-derived base **1** and is based solely on empirical data. According to this model, the enantio-differentiation is caused by a steric repulsion between the epoxide *syn*-γ-substituent and the tertiary pyrrolidine in transition state (TS) I, thus favoring a reaction path *via* the diastereomeric TS II (Fig. 1).

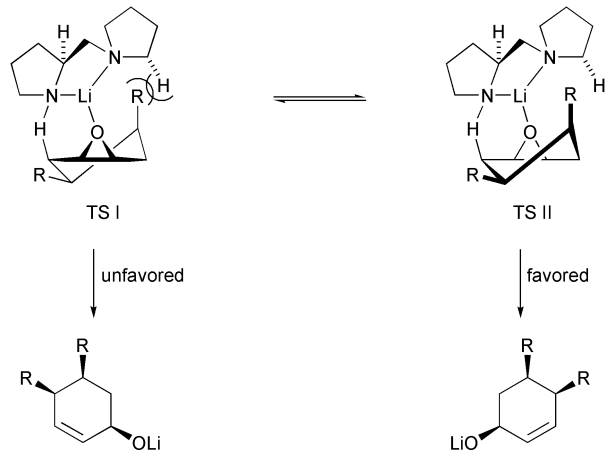


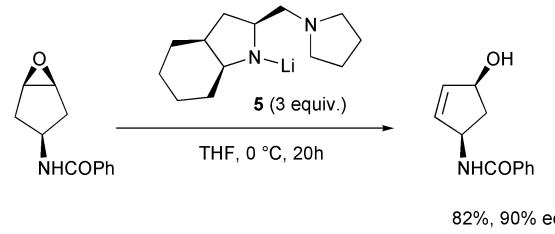
Fig. 1

Recent developments

New bases

To improve the enantioselectivity of the epoxide rearrangement reaction further, a number of structurally more complex diamines have been prepared and successfully applied in combination with different substrates.

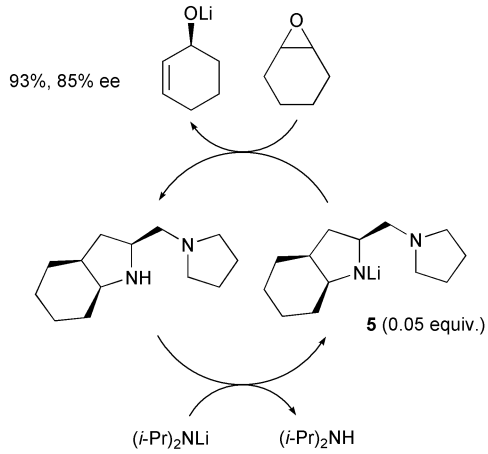
For example, using lithium (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidide (**1**) in THF with DBU as additive, 4-amino-2-cyclopentenol derivatives were obtained in moderate yield (59%) and good selectivities (83% ee). Employing the more complex base **5** in this reaction, the allylic alcohol could be obtained in 82% yield with high selectivity (90% ee) using 3 equiv. of chiral base even without any additive (Scheme 3).[10]



Scheme 3

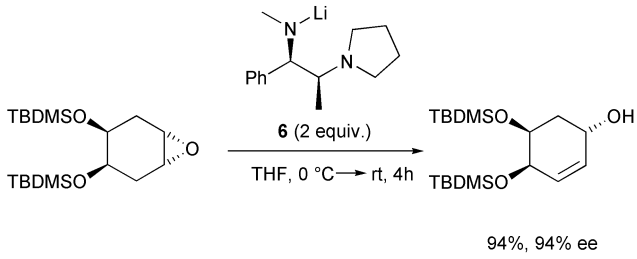
Lithium amide **5** could also be applied in *catalytic* amounts for the rearrangement of a few substrates. With a catalyst loading of 5% together with LDA as stoichiometric base, cyclohexene oxide was rearranged in high yield (93%) with an enantiomeric excess of 85% ee (20 mol% of **5** resulted in 94% ee) (Scheme 4).[11] Already in 1994, Asami had presented the possibility of extending the isomerization protocol to the use of chiral base in substoichiometric amounts.[12]

Chiral diamine (**6**)—easily prepared from norephedrine[13]—was selected because of its structural similarity to Singh's diamine **2**. The simple modification of introducing steric bulk in the form of a methyl group resulted in the rearrangement of a



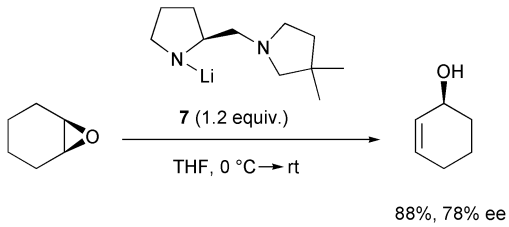
Scheme 4

meso-cyclohexene oxide (Scheme 5) in 94% ee compared to 76% ee with Singh's diamine.[14]



Scheme 5

A new chiral lithium amide base **7**, prepared from (*S*)-proline, was designed by Davidsson[15] *et al.* The base has been used for asymmetric β-deprotonation of cyclohexene oxide to give (*S*)-2-cyclohexen-1-ol in 88% yield and 78% ee (Scheme 6). The

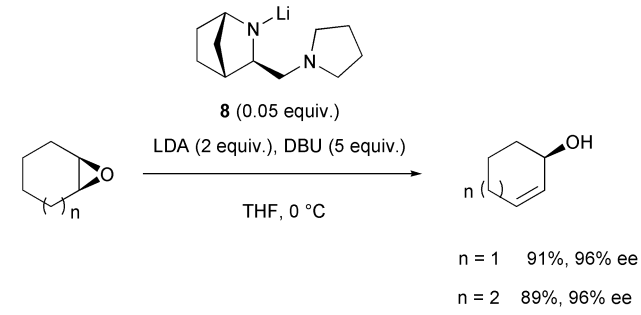


Scheme 6

unsubstituted proline derivative **1** rearranges cyclohexene oxide with similar results (84% yield, 80% ee), which indicates that steric bulk in the 3-position of the tertiary amines has little effect on the outcome of the reaction.

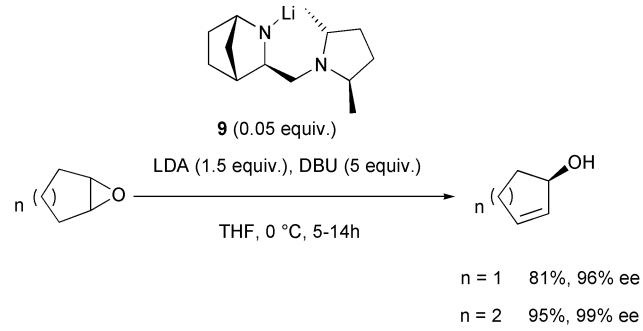
Our group reasoned that lithium amide **8**, having a more rigid backbone compared to lithium amide **1**, would adopt a more ordered TS in the deprotonation reaction. This could give rise to higher asymmetric induction as the result of a more strict discrimination between the enantiotopic protons in the substrate. A straightforward and high-yielding route to **8** was developed and the lithium amide was evaluated in the epoxide rearrangement (Scheme 7).[16,17] It is noteworthy that this system represents one of the very few lithium amide bases that can be used in catalytic amounts.

A further improvement was the utilisation of the (2*R*,5*R*)-dimethylpyrrolidinyl-substituted catalyst **9**, which was highly



Scheme 7

reactive and induced high enantioselectivity and several substrates were rearranged with excellent enantioselectivities. In addition, the use of this sterically more demanding base allowed the first successful, true catalytic rearrangement of difficult substrates such as cyclopentene oxide (81%, 96% ee) (Scheme 8) and (*Z*)-4-octene oxide (80%, 91% ee).[18]



Scheme 8

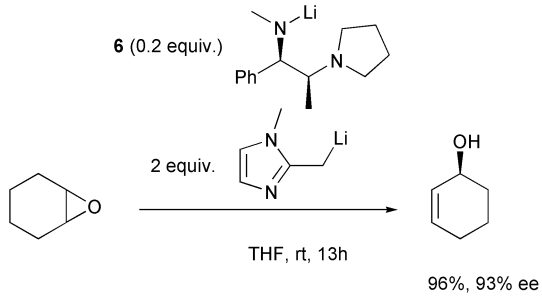
Mechanistic and structural features

It is generally known that aggregation and solvation strongly affect both reactivity and selectivity in lithium-amide mediated reactions. The composition of the activated complex in the rearrangement reaction is not determined fully but some kinetic and computational studies have been performed on the subject.[19,20] For the catalytic epoxide rearrangement reaction, addition of DBU has in some cases been shown to improve the protocol in the aspect of enantioselectivity. The Lewis base additive has been assumed to act as a lithium-amide aggregate suppressant. Supporting this theory is a non-linear effect study where the enantiomeric purity of the chiral lithium amide was varied in the rearrangement of cyclohexene oxide to (1*R*)-cyclohex-2-en-1-ol with or without DBU.[16] In the absence of or with low concentration of the additive, a negative non-linear effect was revealed. However, the negative effect diminished when the amount of DBU was increased.

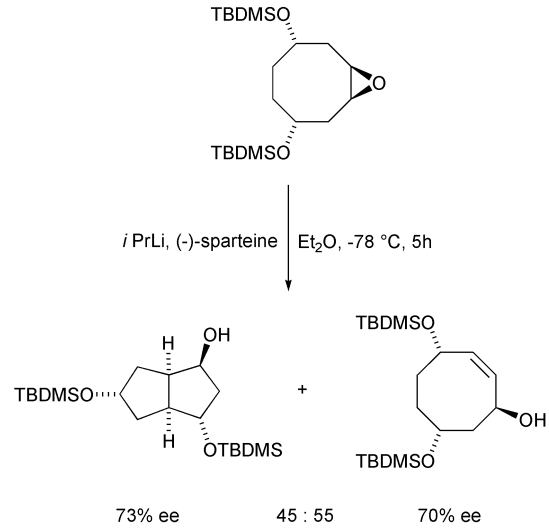
The ability to decrease aggregation is not a feature restricted to DBU but has been indicated for other Lewis base additives as well. However, no additive has been found so far to compete with DBU for efficiency in this particular transformation.[17]

LDA has been the achiral base of choice for the catalytic rearrangement reactions so far. Obviously, LDA is much more potent as base in the deprotonation of diamines compared to epoxides. However, for slow catalytic systems the competing unselective reaction has shown to be fatal for the enantioselectivity in the reaction.[18] Ahlberg *et al.* have found that it is beneficial to replace the commonly used LDA with 2-(lithiomethyl)-1-methylimidazole as a bulk base.[21] Using 20 mol% of the

base **6** earlier described by O'Brien[13] and stoichiometric amounts of 2-(lithiomethyl)-1-methylimidazole they obtained up to 93% ee in the rearrangement of cyclohexene oxide (Scheme 9).



Scheme 9



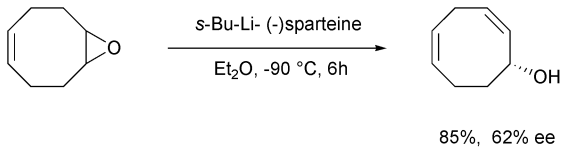
Scheme 11

Selectivity

A few studies on the regioselectivity in the epoxide deprotonation reaction have been performed.[22–24] Also, one alternative explanation to the enantioselectivity in the β-elimination reaction has been introduced to date. Based on a computational study, Ahlberg *et al*. suggest that difference in solvation of the two transition states together with steric interaction between the epoxide ring and the lithium amide backbone are responsible for the asymmetric induction.[25]

New substrates

Cyclooctene oxides are not commonly used substrates for the base promoted epoxide rearrangement but, as shown in Scheme 10, the addition of *meso*-cycloocta-1,5-diene oxide to a 1 : 1 *s*-



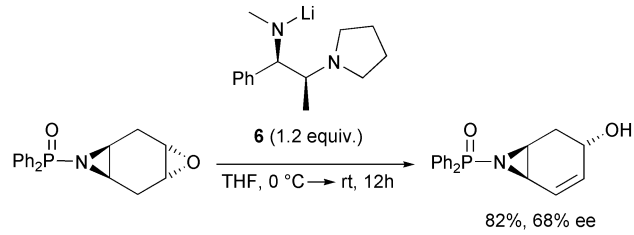
Scheme 10

BuLi–(−)-sparteine mixture at low temperature yielded the allylic alcohol in 85% yield and moderate enantioselectivity (62%).[26]

Other investigations using a mixture of *i*-PrLi and (−)-sparteine for the rearrangement of a different substituted cyclooctaene oxide resulted in a mixture of two different products (Scheme 11).[27] The ratio between the α- and β-elimination products could be strongly influenced by the type of ligand present.

Aziridino cyclohexene oxides were chosen as substrates to probe whether it was possible to rearrange an aziridine to an allylic amine using chiral base. Alternatively, if the aziridine proved to be inert under the reaction conditions, the obtained allylic alcohols would be highly functionalized building blocks for use in synthesis.

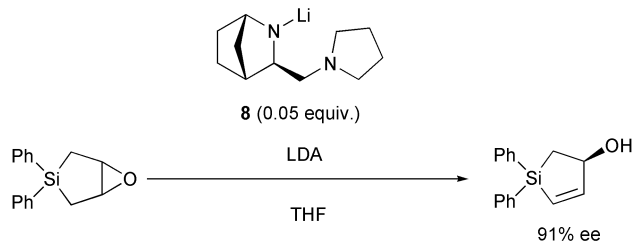
Enantioselective rearrangement of the *cis*-epoxide with chiral base gave the allylic alcohol in moderate 47% ee whilst that of the *trans*-epoxide proceeded with good enantioselectivity (Scheme 12).[28] These results indicate that epoxides rearrange faster than aziridines using chiral lithium amides and that



Scheme 12

aziridines are even compatible with the chiral bases at room temperature.[29]

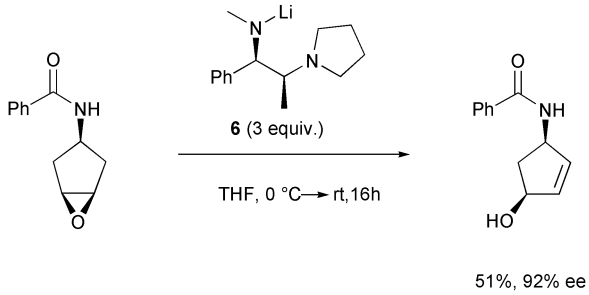
The highly enantioselective base-promoted rearrangement of silacyclopentene oxides is described by Liu and Kozmin.[30] They recently found that the use of diphenylsilacyclopentene oxide in combination with bicyclic amide **8** resulted in a very high level of enantioselectivity of the corresponding allylic alcohol (95% ee). The rearrangement can also be performed efficiently using only a catalytic amount of **8** (5 mol% of catalyst gave 91% ee) (Scheme 13).



Scheme 13

A new substrate class, the 4-aminocyclopentene oxide derivatives, were investigated in the rearrangement reaction since the products, 4-amino-2-cyclopentenol derivatives, can be employed as useful intermediates for the syntheses of carbocyclic nucleosides and their analogues. By using 3 equivalents of the chiral base **6**, O'Brien *et al*. presented a smooth

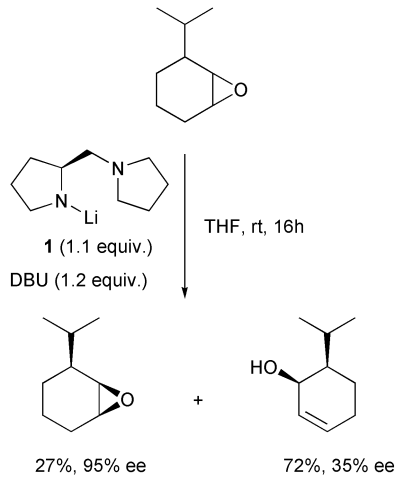
rearrangement of an 4-aminocyclopentene oxide to generate the allylic alcohol in 51% yield and 92% ee (Scheme 14).[13]



Scheme 14

Kinetic resolution

The kinetic resolution of racemic *cis*-3-*i*-propylcyclohexene oxide was examined by Asami[31] *et al.* using chiral lithium amide **1**. By using 1.1 equivalents of chiral base, the optically active *cis*-3-*i*-propylcyclohexene oxide was obtained in high ee (95%) but in low yield (27%), while the corresponding allylic alcohol showed only 35% ee (72% yield) (Scheme 15).

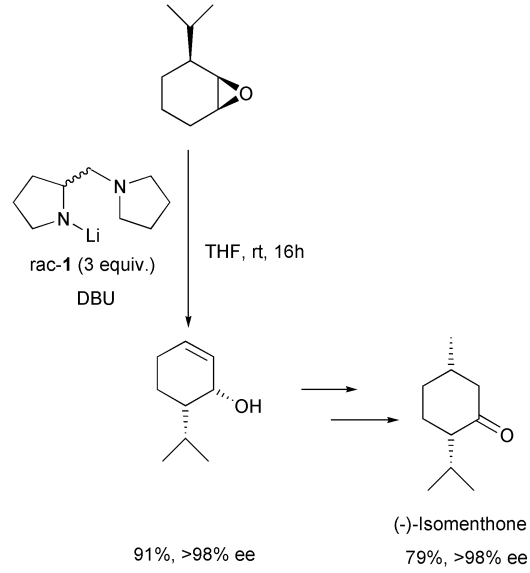


Scheme 15

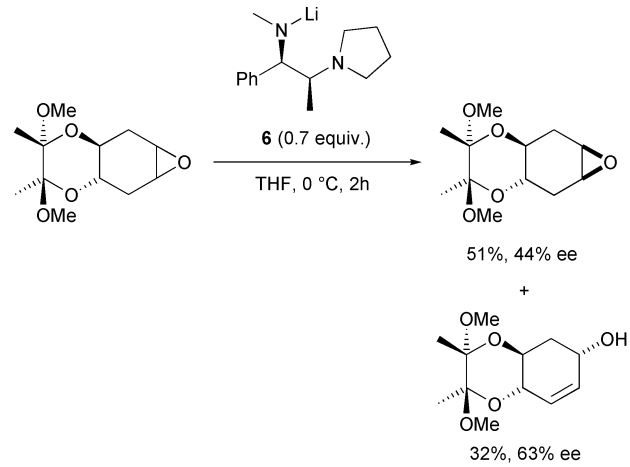
The kinetic resolution protocol provides a method for the synthesis of chiral multi-substituted cyclohexene derivatives by subsequent stereoselective reactions as outlined in Scheme 16 for the synthesis of (−)-isomenthone.[31]

The first example of a kinetic resolution on a chiral 4,5-dihydroxycyclohexene oxide is illustrated in Scheme 17. Reaction of racemic 4,5-dihydroxycyclohexene oxide with 0.7 equivalents of the chiral lithium amide base **6** generated the allylic alcohol in moderate yield but good enantioselectivity and recovered 4,5-dihydroxycyclohexene oxide in good yield but moderate enantioselectivity.[32]

The kinetic resolution of an acyclic epoxide and 1-methyl substituted cyclohexene oxide under catalytic reaction conditions has been described using only 5 mol% of the chiral lithium amide **8**. To obtain both the unreacted epoxide and the allylic alcohol product in high enantioselectivity the reaction was



Scheme 16



Scheme 17

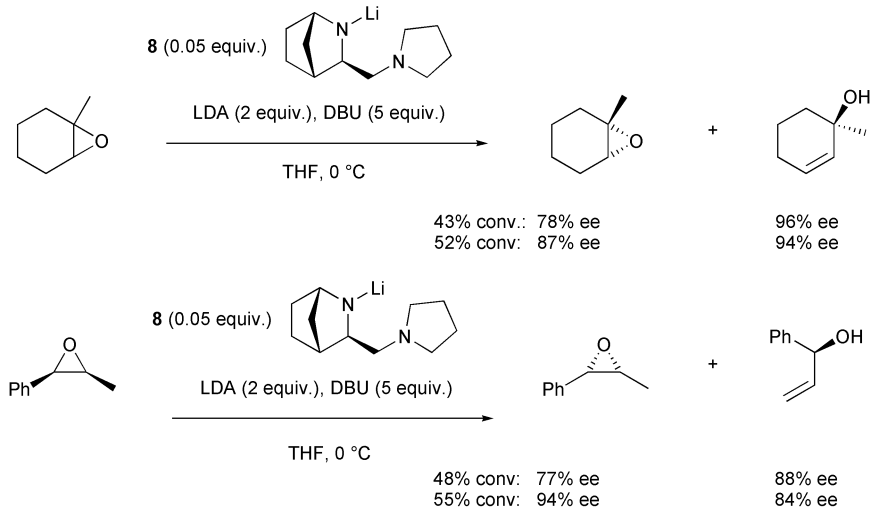
aborted either shortly before or after 50% conversion (Scheme 18).[17]

New applications

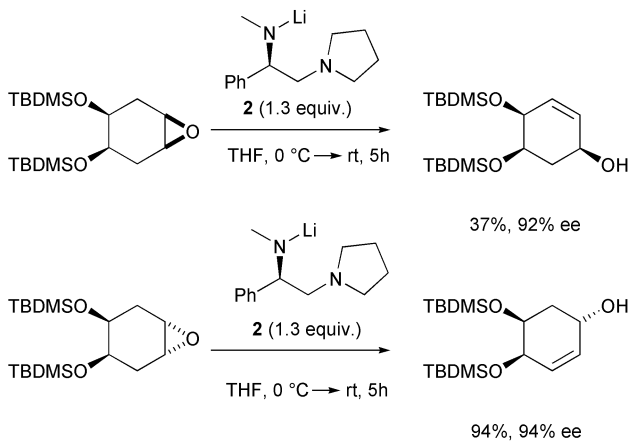
O'Brien and Poumellec have reported a new route to bis-protected 4,5-dihydroxycyclohex-2-enone.[33] The key step in this synthesis is the chiral base promoted rearrangement of *trans*- and *cis*-epoxide (Scheme 19). The method can be used to prepare for the first time either enantiomer of the 4,5-dihydroxycyclohex-2-enones.

Another application for the chiral base promoted rearrangement is the asymmetric synthesis of 4-aminocyclopent-2-en-1-ols as intermediates for carbocyclic nucleoside analogues (Scheme 20). The approach involves the stereoselective preparation of *cis* 4-amino-substituted cyclopentene oxides and subsequent chiral base mediated rearrangement to the corresponding allylic alcohols in good yields and excellent enantioselectivities.[34]

The chiral base promoted rearrangement of *meso* epoxides to the corresponding allylic alcohols provides a key intermediate

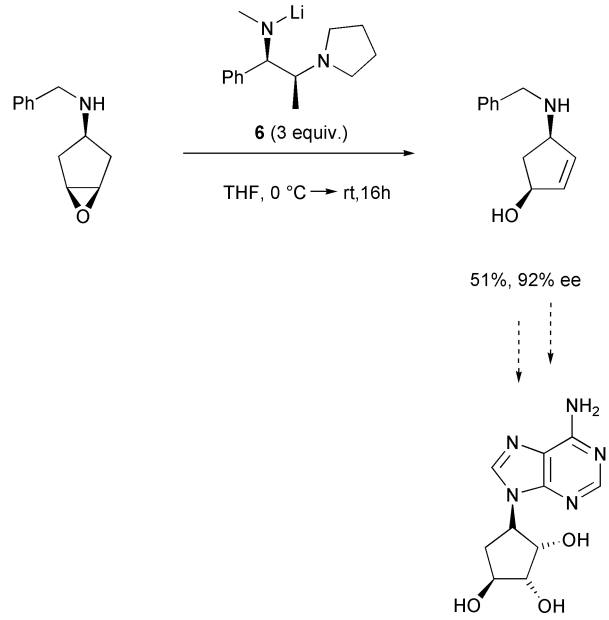


Scheme 18

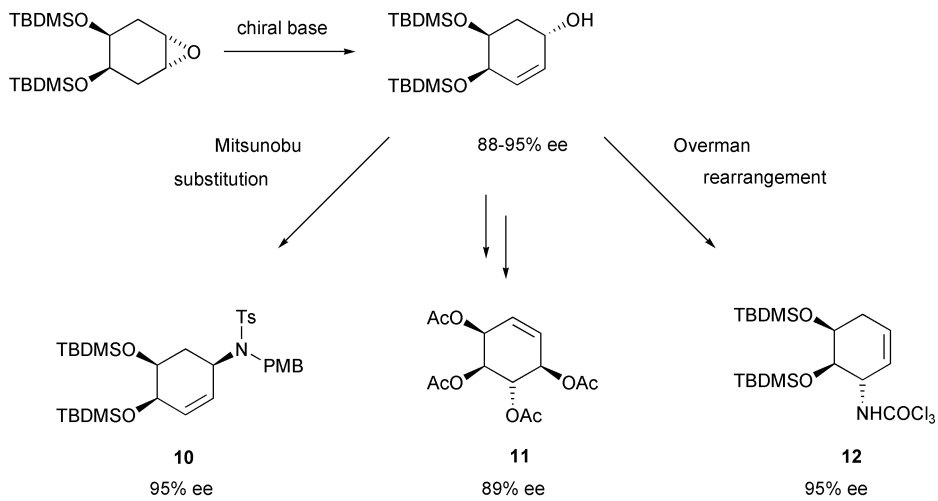


Scheme 19

for the synthesis of aminodeoxyconduritols and conduritol F (Scheme 21).[35] To convert the allylic alcohol into some aminodeoxyconduritols (**10** and **12**) a Mitsunobu approach or an Overman rearrangement is used. Conversion into a chiral eneone and further elaboration *via* α-hydroxylation and a



Scheme 20



Scheme 21

stereoselective reduction completes the synthesis of the tetra-acetate of conduritol F (**11**) in high yield.

Outlook

The recent development of the chiral base promoted rearrangement of epoxides has resulted in a number of improvements in terms of selectivity, scope and the development of truly catalytic methods. Nevertheless the reaction is still challenging since, a chiral catalyst, able to transform cleanly in high enantioselectivity a range of different epoxides with the consumption of no other additives, remains to be found.

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