Pergamon

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Tetrahedron 59 (2003) 9695–9700

TETRAHEDRON

A DFT exploration of the enantioselective rearrangement of cyclohexene oxide to cyclohexenol

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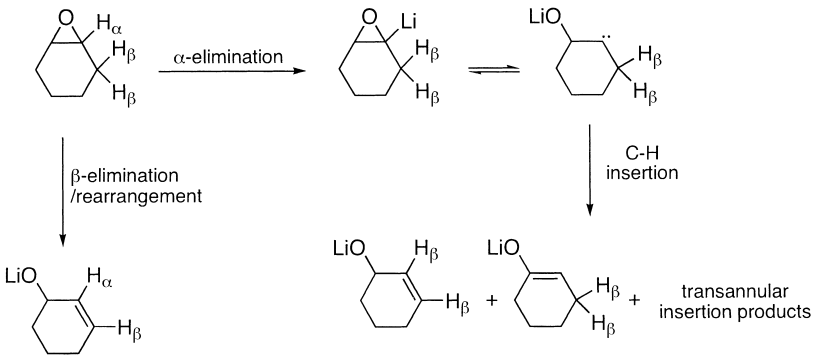
Received 2 September 2003; revised 26 September 2003; accepted 1 October 2003

Abstract—In this paper, we present computational results for the (1*S*,3*R*,4*R*)-3-(pyrrolidinyl)-methyl-2-azabicyclo[2.2.1]heptane mediated rearrangement of cyclohexene oxide. The results nicely explain the differences in enantioselectivities between catalytic and stoichiometric mode between different ligands, and provides a rational for the identification of non-stereospecific background reactions as the major cause of decreased enantioselectivity in catalytic reactions for sterically hindered diamines.

1. Introduction

Optically active 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 is 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 enantioenriched 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, they opened up for further research in the area. The scope of the reaction has increased markedly during the last 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[2] 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.[3–5]

Epoxides react with strong, non-nucleophilic bases, such as lithium amides, by deprotonation in either α- or β-position.[6] Abstraction of the α-hydrogen gives rise to a reactive carbene intermediate, which undergoes C–H insertion to produce allylic alkoxide, enolate, and/or other insertion products. 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



Scheme 1.

Keywords: α-deprotonation; enantioselectivity; cyclohexene oxide.
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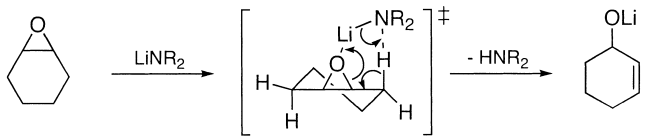
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.013

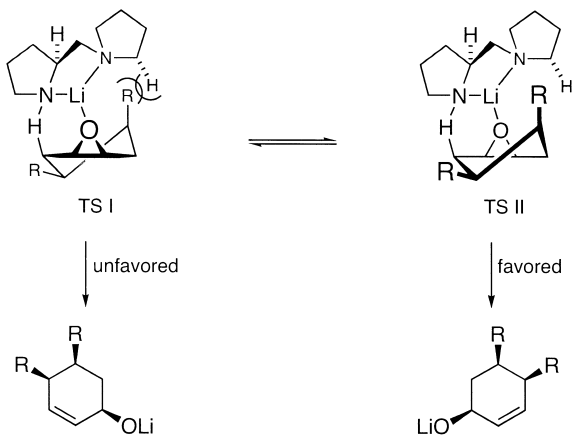
relative rates of α- and β-deprotonation are primarily substrate dependent, but in some cases the choice of base and reaction conditions could affect the regioselectivity in the reaction.

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 disfavored 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.

There are very few studies of the factors underlying the enantioselectivity of the reaction in the literature. One paper describes the enantioselectivity observed when using the proline-derived base and is based solely on empirical data.[7] According to this model, the enantiodifferentiation is caused by a steric repulsion between the epoxide and the tertiary pyrrolidine in the transition state, thus favoring a reaction path via the diastereomeric TS II (Scheme 3).



Scheme 3.

In a paper by Nilsson Lill et al.[8] the reaction has been studied by semi-empirical and density functional methods. Their findings support the enantioselectivity model proposed by Asami but add to the explanation a differential solvation of the diastereomeric transition states as an important factor. We have presented a preliminary account of the reaction between a model of the litiated diamine **1** and cyclohexene oxide.[9] This density functional theory study emphasizes the steric repulsion between the pyrrolidine and the substrate in the disfavored transition state. In this paper, we present computational results for the (1*S*,3*R*,4*R*)-3-(pyrrolidinyl)-methyl-2-azabicyclo[2.2.1]heptane mediated rearrangement of cyclohexene oxide. The results nicely explain the differences in enantioselectivities between catalytic and stoichiometric mode between different ligands, and provides a rational for the identification of non-stereospecific background reactions as the major cause of decreased enantioselectivity in catalytic reactions for sterically hindered diamines. The results from these calculations have been previously used as a background for optimizing the protocol used for epoxide rearrangement using the azanorbornyl diamines.[10]

2. Computational methods

2.1. General

All calculations reported in this work were conducted using the Gaussian 98 program.[11] Geometry optimizations were performed using the B3LYP hybrid functional,[12] together with the Dunning–Huzinaga valence double-ζ basis set (d95v), a reasonably large basis set considering the large size of the model systems.[13] Transition states were located using initial force constants from HF/3-21G or HF/STO-3G as starting point for traditional transition state optimizations using the Berny algorithm.[14] Transition states were characterized by normal mode analysis using B3LYP/d95v with each transition state showing one imaginary frequency. Due to the large size of the model systems, normal mode analysis were not carried out for the ground states. Final energies were determined using B3LYP together with the 6-311+G(d,p) basis set. Unless otherwise stated, energies in the text refer to this level of theory, with zero-point energy corrections included in the comparisons of transition states. Pre-optimization and initial conformational analyses were performed using HF/3-21G. Apart from the chiral ligands evaluated in the computational study, shown in Figure 1, dimethyl ether was used to model THF and *N*-methyl formimine was used as a simple model for DBU.

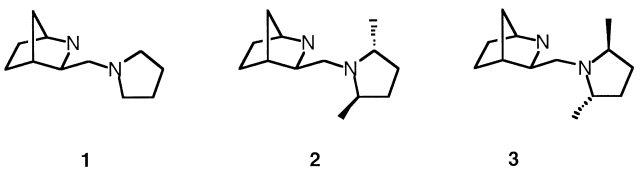


Figure 1. Ligands analyzed in the computational study.

2.2. Enantioselectivity

Starting conformations of transition states for ring-opening of cyclohexene oxide were generated using a preliminary transition state force field (MM3*) developed for Macromodel 6.5 using data from B3LYP/6-31G* calculations.[15] Clustering of conformations resulted in two major orientations of the pyrrolidine nitrogen with respect to the chelate ring[16] and two different envelope conformations of the same ring. Thus, four different conformers for each ligand and diastereomeric transition state were subjected to quantum chemical calculations (HF/3-21G followed by B3LYP/d95v).

3. Results and discussion

3.1. Dimerization mode

In a study of non-linear effects on the enantioselectivity in

the rearrangement of cyclohexene oxide to cyclohexenol using diamine **1** with 10 equiv. of DBU as co-solvent, the reaction was concluded to occur between a monomeric lithium amide complex and the epoxide. Reduction of the addition of DBU induced a non-linear effect, indicating the appearence of unequal amounts of homo and hetero dimers in the reaction mixture. To investigate the possibility that dimers are present as active catalysts in the reaction, we studied the preferred dimerization mode, the dimer dissociation energy, and the activation energy for a rearrangement effected by the dimer.

Lithium amides are prone to form aggregates in solution and this is known to alter both reactivity and selectivity.[17] To account for the aggregation state of lithiated diamines **1**–**3** in the absence of DBU co-solvent, when evaluating relative rates between different diamines, we started this investigation by determining the preferred dimerization mode. Two different types of lithium amide dimers were evaluated using the minimal model ligand **4** (Fig. 2). The conformational space of the 5-membered chelate ring was evaluated, resulting in complexes possessing C_2- as well as C_1-symmetry. Dimer **A** was found to be 39 kJ/mol more stable than **B** at B3LYP/d95v and is hence the major dimer in the reaction mixture. This result is in line with results of Arvidsson et al.[18]

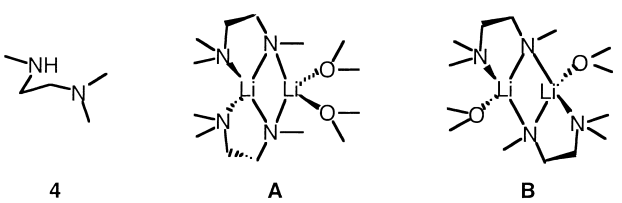


Figure 2. Evaluation of the mode of dimerization.

3.2. Dimer dissociation energies

Dissociation energies, as defined in Figure 3, were calculated for ligands **1**–**3** using dimerization mode **A**, predicted to be the preferred ligand arrangement in the preceding analysis. The conformation of the 5-membered chelate ring was used as found in the global minimum in the conformational search of dimer **A** above. In dimers involving ligands **1**–**3**, the pyrrolidines are in close contact and a conformational analysis was therefore, performed.

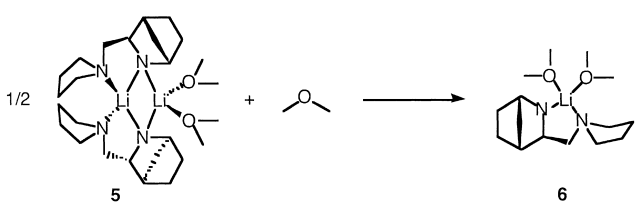


Figure 3. Evaluation of the dimerization tendency.

As seen in Table 1, dimerization is only energetically favorable for diamine **2**. However, dimerizations of lithium amides are known to be entropy driven, as indicated by the change in molecularity of the reaction in Figure 3. Thus, dimerizations of all lithium amides of **1**–**3** are likely to occur in the reaction media in the absence of DBU. Seemingly, the least stable dimer would be (Li-**1**)$_2$, a fact

Table 1. Dimer dissociation energies (kJ/mol)

Ligand	HF/3-21G	B3LYP/d95v	B3LYP/6-311+G(d,p) //B3LYP/d95v
1	0	−15	−23
2	29	12	3
3	25	2	−9

that could hypothetically render this species less dependent on DBU as co-solvent. However, this seems to be an oversimplification of the kinetics of the reaction(Fig. 4).

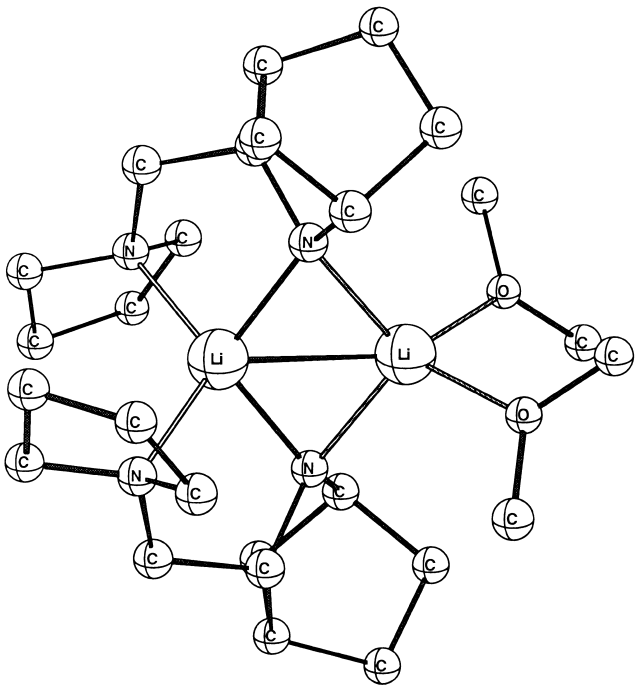


Figure 4. Global minimum of the dimer [Li-**1**-(Me_2O)]$_2$ at B3LYP/d95v.

According to our calculations, the dimers are inactive in the reaction. Using dimer **5** without solvent, we have determined the activation energy to 76 kJ/mol (Fig. 5). This will result in a dramatically slower epoxide rearrangement for the dimer compared to the monomer (vide infra). All

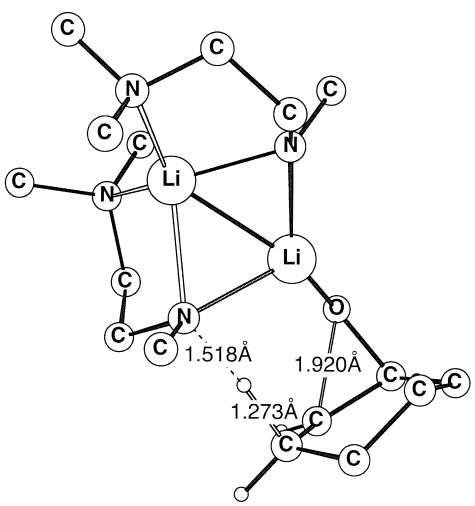


Figure 5. The dimer transition state for rearrangement of cyclohexene oxide.

attempts to optimize a transition state for an open dimer, as postulated by Collum and co-workers,[19] resulted in a contraction of the structure to the structure depicted in Figure 5.

3.3. α-Deprotonation versus β-elimination

α-Deprotonation may seem exotic but is in fact the major pathway for some combinations of base and epoxide,[20] leading to either allylic alcohols, ketones or other products emerging from C–H insertion. Considering the high selectivity and yield of cyclohexenol from cyclohexene oxide, the major product is likely to be formed via β-elimination. However, using reaction conditions less enantioselective, or with lower yields, α-deprotonation could be an alternative. To evaluate the feasibility for α-deprotonation, we studied the reaction between lithiated **1** and cyclohexene oxide.

Surprisingly, the activation energy for α-deprotonation was found to be only 9 kJ/mol higher in Gibbs free energy than the barrier for β-elimination (B3LYP/6-311+G(d,p)//B3LYP/d95v). Thus, it is very likely that some ligand/substrate combinations that give rise to slow β-eliminations could switch to α-deprotonation. According to the calculations, the steric interactions in the transition state for α-deprotonation is less pronounced (Fig. 6) and the enantioselectivity is switched in favor of *S*-cyclohexenol ($\Delta\Delta G^{\ddagger}$=6 kJ/mol at B3LYP/6-311+G(d,p)//B3LYP/d95v).

3.4. Enantioselectivity

A correct prediction of the enantioselectivity would serve two purposes. First, the mechanism determined for the reaction will be supported, and secondly, the calculated geometries could help understanding the enantioselectivity process. This, in turn, will enable design of new efficacious

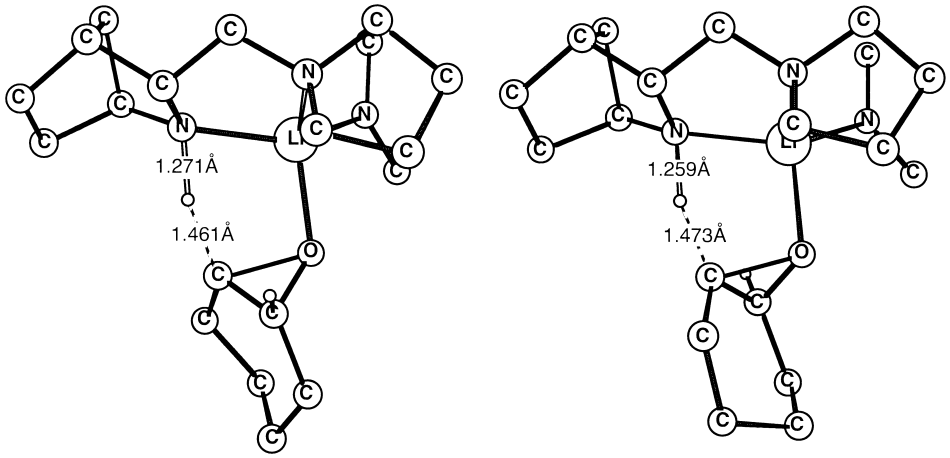


Figure 6. Two diastereomeric transition states for α-deprotonation/epoxide opening showing reduced steric interactions between the diamine and substrate.

Table 2. Calculation of relative diastereomeric transition state Gibbs free energies (kJ/mol)[a]

Ligand	B3LYP/d95v	B3LYP/6-311+G(d,p)//B3LYP/d95v	Pred ee (%)	Obs. ee stoich. (%)[b]	Obs. ee cat. (%)[b]
1	7.8	8.6	94.9	97/97	93/70
2	7.5	7.7	91.4	99/99	99/90
3	6.5	6.7	87.6	86/81	44/20

[a] Thermal correction to Gibbs free energy from B3LYP/d95v. *T*=25°C.
[b] 10 equiv. DBU/0 equiv DBU. Data collected from Ref. 21.

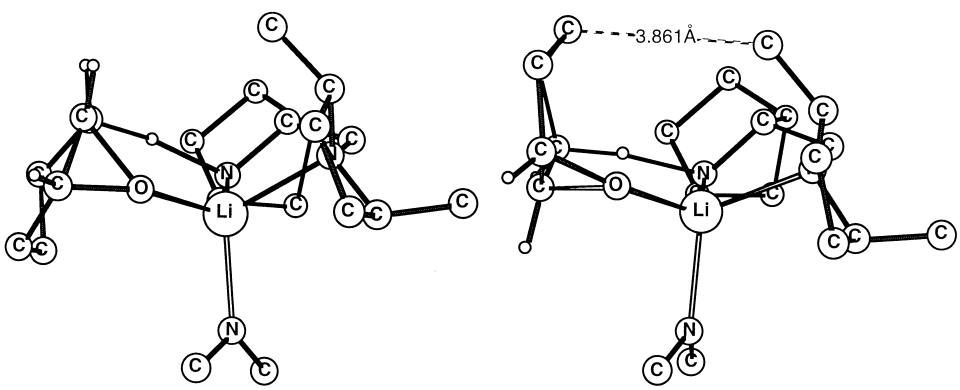


Figure 7. Diastereomers of the transition state for the β-elimination effected by diamine **3** showing increased steric interactions between the substrate and the 2-(*S*)-pyrrolidinyl substituent.

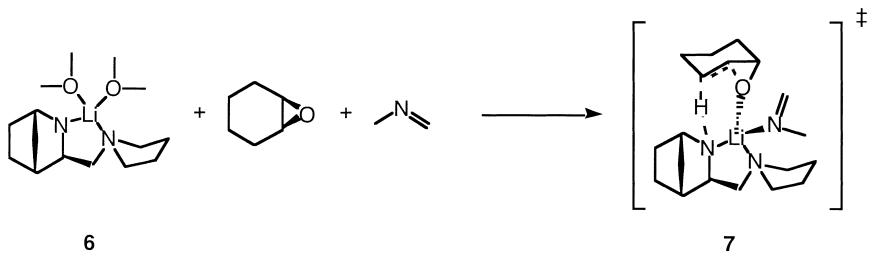


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Figure 8. Evaluating transition state energies.

Table 3. Activation energies for β-elimination (kJ/mol)

Ligand	HF/3-21G	B3LYP/d95v	B3LYP/6-311+G(d,p) //B3LYP/d95v	Conversion after 2 h (%)[a]
1	64	19	43	22/45
2	66	20	44	27/55
3	77	26	51	7/19

[a] Stoichiometric reaction without addition of DBU added/with addition of 10 equiv. DBU. Data from Ref. 21.

diamines and diamine/substrate combinations. Evident from Table 2, all diamines are predicted to give high enantioselectivities in stoichiometric reactions.

Considering the optimized diastereomers of the transition state for the β-elimination effected by diamine **3**, the interaction between the 2-(*S*)-pyrrolidinyl substituent and the substrate is interesting (Fig. 7). The 2-(*S*)-pyrrolidinyl methyl group interacts with a methylene of the substrate in the pro-(*S*) transition state, suggesting a selective slowdown of this diastereomeric reaction pathway. This interpretation contradicts the speculations put forward earlier by Bertilsson et al.[21] However, the hypothetical gain in enantioselectivity is absent and is instead manifested in a decreased reaction rate for this diamine (vide infra). A decrease in reaction rate due to increased steric interactions could increase the importance of unselective reaction paths such as α-deprotonation followed by formation of allylic alcohol or β-elimination effected by bulk base.

3.5. Activation energies for the β-elimination pathway

Activation energies were calculated using a bis(dimethylether) lithium amide complex as the ground state. This ground state was somewhat arbitrarily chosen as the resting state of the catalyst is not yet established. We have made efforts to characterize the rate determining step by kinetic measurements and the reaction seem to be first order in both epoxide and diamine. However, our data are not of appropriate quality for excluding all other alternatives. In a more accurate study performed by Olsson et al. the kinetics of the pyrrolidine analogue of **1** was determined and the reaction was found to be first order in cyclohexene oxide.[22] In the following we postulate the transition state depicted in Figure 8 to be rate determining. The observed rate of the reaction will then also be affected by the dimerization tendency as well as the rate of regeneration of the catalyst.

Table 3 shows the calculated activation energies for β-elimination mediated by the lithiated diamines **1**–**3**. Apparently, the low reactivity reported[21] for diamine **3** is due to a higher activation energy for β-elimination. This supports the hypothesis put forward above about interference from unselective reaction paths in case of diamine **3**. These findings encouraged us to develop the successful method of slow addition of the stoichiometric base to avoid β-elimination effected by the bulk base.[6]

4. Conclusions

To conclude, the suggested reaction mechanism has been confirmed computationally. This mechanism can both predict the major enantiomer of the reaction as well as rationalize the experimental difference in rate between the considered diamines. The energy differences between the diastereomeric TS do not correspond to the experimental catalytic enantioselectivity. The calculated differences in rates suggested that a non-stereospecific background reaction caused the drop in selectivity, not difference in intrinsic enantioselectivity for the ligands. This was the idea behind the experimentally tested and better performing slow-addition protocol. Dimers are inactive according to the calculations. Dimerization energies do not correlate with the enantioselectivity. Thus, in case DBU is used as co-solvent, the dimerization does not seem to be a problem.

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