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Tetrahedron 64 (2008) 575–581

Tetrahedron

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MM3 force field prediction of the enantioselective preference in the asymmetric synthesis of a chiral 2-cyclohexen-1-ol using a chiral lithium amide reagent

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Received 27 August 2007; received in revised form 26 October 2007; accepted 29 October 2007

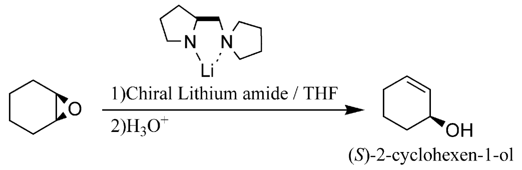
Abstract

Enantioselective preference in the asymmetric synthesis where cyclohexene oxide is transformed enantioselectively to chiral (*S*)- or (*R*)-2-cyclohexen-1-ol by the reaction with the appropriate chiral lithium amide reagent has been evaluated theoretically using the MM3 force field. The plausible possible structures for each precursor (reaction intermediate complex) leading to a (*S*)- or (*R*)-2-cyclohexen-1-ol have been optimized with the extended MM3 force field applicable to the lithium amide functional group, and the populations of their (*S*)- or (*R*)-reaction intermediate complexes at an ambient temperature (298 K) were calculated. The initial structure for evaluating the reaction intermediates of this asymmetric synthesis was constructed on the basis of the optimized ab initio transition state structure (MP2/6-31+G*) comprising lithium amide $LiNH_2$ and propene oxide. To the thus obtained transition state structure composed of $LiNH_2$ and propene oxide, the other remaining Cartesian coordinates for the actual reaction intermediates composed of the chiral lithium amides and cyclohexene oxide were added to make the reaction intermediate structure. The conformational search for the reaction intermediate has been carried out by using the Stochastic search Algorithm, and the optimized geometries and their conformational energies (steric energies) have been calculated by the MM3 force field. The populations calculated from the conformational energies of the reaction intermediate leading to the (*S*)- or (*R*)-2-cyclohexen-1-ol were shown to be linearly well correlated with the experimentally reported enantiomer excess (% ee) values. The critical factors to control the enantioselectivity were investigated on the basis of the optimized structures of the reaction intermediate complexes. The MM3 force field approach was shown to be applicable to the theoretical evaluation of the enantioselectivity and be useful for designing a new functional chiral lithium amide reagent for the asymmetric synthesis.

Keywords: MM3 force field; Asymmetric synthesis; Chiral lithium amides; Enantioselective deprotonation

1. Introduction

It is reported that chiral lithium amide reagents derived from (*S*)-proline such as lithium (*S*)-2-[(pyrrolidin-1-yl)methyl]pyrrolidide can react with cyclohexene oxide to produce (*S*)-2-cyclohexen-1-ol with 77% ee enantioselectively by elimination of the β-proton of the epoxide ring[1] (Scheme 1).



Scheme 1.

What is the essential factor controlling the enantioselectivity in this asymmetric reaction? The structure of the reaction intermediate complex formed between the lithium amide reagents and the substrate cyclohexene oxide in ether solvent

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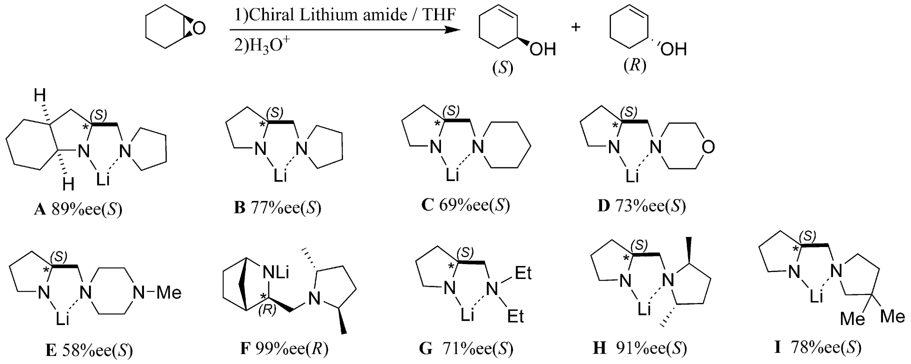
doi:10.1016/j.tet.2007.10.110



Scheme 2. Reported % ee values in the asymmetric syntheses using lithium amide reagents **A**–**I**. Configuration at the chiral carbon next to the lithium amide nitrogen is shown.

was investigated experimentally by using NMR[2] (^{13}C NMR, ^{6}Li NMR, ^{6}Li EXSY), and the intra-exchange process of the coordinated N-atom ligands is reported to occur under the experimental conditions. Judging from the experimentally determined enantioselectivity[1,3,4] in terms of % ee shown in Scheme 2, the unique structure of the chiral lithium amide reagent which can form a special chiral environment at the transition state is assumed to be important in giving rise to a strong enantioselectivity to form the (*S*)- or (*R*)-product.

In order to clarify the steric effects due to the substituents in the chiral reagents for the asymmetric synthesis in detail, a theoretical approach has been carried out by using semi-empirical (PM3) or ab initio molecular orbital calculations.[5] However, the molecular mechanics (MM3) or force field approach may be more practical than the molecular orbital approach because of the calculation speed in the process of the exhaustive conformational search of the reaction intermediate complex when the size of the system for the asymmetric reaction is taken into account.

In this work, the plausible reaction intermediate model applicable to evaluate the enantioselectivity in the chiral 2-cyclohexen-1-ol asymmetric synthesis using the chiral lithium amide reagent was examined. A basic concept to make a plausible intermediate model is as follows.

(1) The transition state of a model system for the proton abstraction reaction by strongly basic lithium amide nitrogen is evaluated by MP2/6-31+G* level ab initio calculations. The model is comprised of lithium amide ($LiNH_2$) and propene oxide to mimic the actual asymmetric synthesis reaction as shown in Scheme 1.
(2) The thus optimized transition state structure is adopted as a framework of the intermediate model because it contains essential geometrical parameters reflecting the characteristics intrinsic to the transition state. By adding remaining parts existed in the actual system composed of the chiral lithium amide and cyclohexene oxide to this transition state structure, an initial guess of the structure of the plausible intermediate model can be made.
(3) In the geometry optimization process of the intermediate model by the MM3 calculations, essential geometrical parameters of the transition state have been fixed to simulate the transition structure as much as possible.

According to this basic concept, conformational search by the MM3 force field was carried out extensively on the reaction intermediate models to evaluate the optimized structures and conformational energies of the precursors leading to the (*S*)- or (*R*)-product. The calculated population values of the reaction intermediates leading to the (*S*)- or (*R*)-product were shown to be well correlated with the experimentally determined % ee values.

2. Constructing the appropriate reaction intermediate model for the asymmetric synthesis of a chiral 2-cyclohexen-1-ol

As this asymmetric reaction proceeds as a kinetically controlled process, an orthodox theoretical approach to estimate the enantioselectivity is to calculate the transition state (TS) structure and its energy by appropriate theoretical methods (usually a quantum mechanical (QM) calculation). Application of the molecular mechanics (MM) calculations to evaluating the TS structure is not general, or at least is rather limited because force field parameters intrinsic to the TS are hard to determine definitely. The standard approach of the MM calculations in a structural study is to predict the geometries of the local energy minima rather than the local saddle points (TS). Therefore, we have to take an alternative method to evaluate the TS structure and its conformational energy when we use the MM approach. Taking into account the accuracy, speed, and the size of the calculational model to be handled in this case, a useful approach might be to try to find an appropriate reaction intermediate (local minimum) structure which is located close to the transition state using the MM3 force field, assuming that the Hammond's postulate[6] is valid (Fig. 1).

It is an essential point to build a plausible reaction intermediate complex model in which the intrinsic structural characteristics of the TS are reflected. To do so, essential geometrical parameters of the TS model on this asymmetric synthesis should first be evaluated by accurate ab initio calculations including electron correlation. Based on the optimized TS geometry, the actual reaction intermediate complex composed of chiral lithium amide and cyclohexene oxide was constructed. In the process of constructing this complex, important geometrical parameters inherent to the transition state were fixed to represent the nature of the transition state

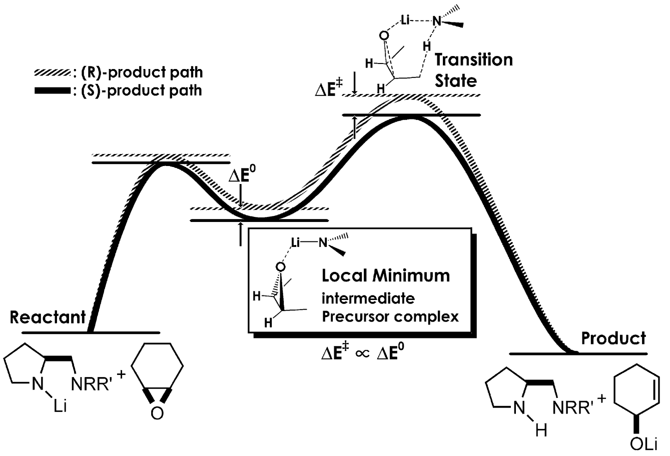
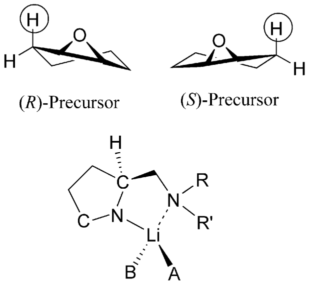


Figure 1. Schematic representation how we evaluate enantioselectivity on the asymmetric synthesis by using the MM3 force field calculations on the basis of Hammond's postulate.

correctly.[7] Though a hybrid (QM/MM) theoretical method such as (ONIOM)[8] is available now, the MM approach may be more practical than the hybrid method when the size of the system and the calculation speed are taken into account under the current computational environment.

In a previous communication[9] on the MM3 prediction of the enantioselectivity for the asymmetric synthesis of a chiral 2-cyclohexen-1-ol, the reaction intermediate was constructed from the chiral lithium amide, cyclohexene oxide, and tetrahydrofuran (THF) as a reaction solvent. While the MM3 calculation was able to reproduce the experimental enantioselectivity tendency correctly, every possible reaction intermediate complex was not taken into account (vide infra) in the theoretical investigation. In principle, all possible reaction intermediate complexes should be considered in the MM calculations. What are the requisite molecules for construction of the reaction intermediate (lithium amide reagent, cyclohexene oxide (substrate), and solvent)? Should the lithium amide reagent be treated as a dimer or as a monomer? How many and what kind of geometrical parameters obtained for the TS model should be fixed in the reaction intermediate model? These are all points to be considered in order to appropriately construct the reaction intermediate model. They are discussed in detail below.

In order to construct appropriate reaction intermediate complexes, a model similar to that adopted by Ahlberg's[10] group was adopted. In this model, an axially oriented β-hydrogen[11] atom of the epoxide ring of cyclohexene oxide is assumed to be eliminated by the strongly basic lithium amide nitrogen atom in the reaction intermediate complex. As shown in Figure 2, there are two types of enantiotopic β-hydrogen atoms, classified as (*R*)-precursor and (*S*)-precursor, dependent on their locations in the cyclohexene oxide. Two plausible attacking routes by the chiral lithium amide reagent to the enantiotopic β-hydrogen atom are considered (top face attack [coordination-site A] or bottom face attack [coordination-site B]) because the lithium amide functional group has a planar geometry. Therefore, there are four types of reaction intermediate complexes labeled (*R*)-precursor: Type 1, (*S*)-precursor: Type 1, (*R*)-precursor: Type 2, and (*S*)-precursor: Type 2, respectively, as shown in Figure 3. These four precursor types will hereafter be called (*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2**, respectively.

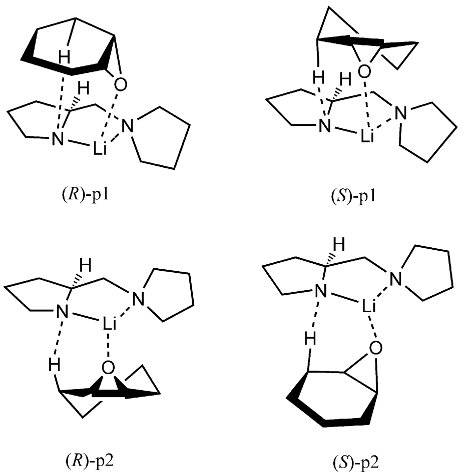


Type 1 : A=cyclohexene oxide, B=THF
Type 2 : A=THF, B=cyclohexene oxide

Figure 2. Possible coordinating sites of the chiral lithium amide reagent with regard to the coordination of the enantiotopic proton ((*R*)- or (*S*)-precursor) and solvent (THF).

An overview of the four types of reaction intermediate complexes is as follows. (*R*)-**p1** or (*S*)-**p2** have structures where only a small part of the cyclohexene oxide ring is overlapped by N–Li bond of the lithium amide reagent in a perpendicular fashion. On the contrary, a large amount of the cyclohexene ring is superimposed perpendicularly on the lithium amide reagent in the (*S*)-**p1** or (*R*)-**p2** complexes. Thus, the (*R*)-**p1** and (*S*)-**p2** complexes are sterically favorable ones, and (*S*)-**p1** and (*R*)-**p2** complexes are rather sterically congested. This steric repulsion (van der Waals interaction) between cyclohexene oxide and lithium amide reagent is assumed to have a large effect on enantioselectivity.

In the earlier MM3 approach[9] to find appropriate reaction intermediate complexes, only (*R*)-**p2** and (*S*)-**p2** complexes were considered to be plausible, because Type 1 complexes were found to be simple complexes rather than reaction intermediate complexes leading to the transition state. This problem may come from an inadequate intermediate complex



(*R*)-p1 (*S*)-p1

(*R*)-p2 (*S*)-p2

Figure 3. Plausible reaction intermediate complexes comprising of the chiral lithium amide reagent and cyclohexene oxide.

structure having been adopted. It is very important to find appropriate reaction intermediate complexes so that essential geometrical parameters intrinsic to the transition state can be properly incorporated in the model. In this work, essential geometrical parameters for the transition state of this asymmetric synthesis have been evaluated by the MP2/6-31+G* level transition state calculations on the $LiNH_2$–propene oxide model system, and all four reaction intermediate complexes were adopted as reaction intermediate complexes in the MM3 force field calculations.

3. Essential geometrical parameters of the transition state

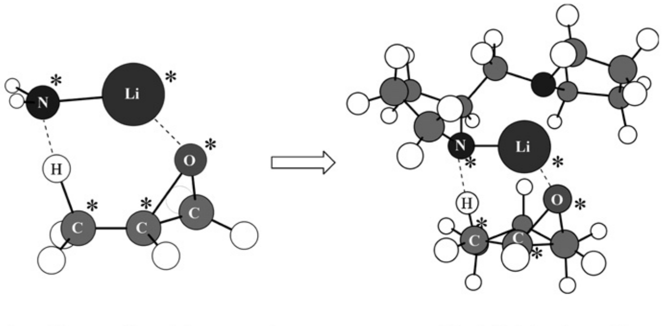
The optimized transition state (TS) structure composed of the $LiNH_2$ and propene oxide with MP2/6-31+G* ab initio calculations is shown in Scheme 3, and essential geometrical parameters of the transition state for the β-proton abstraction process by the chiral lithium amide reagent are also summarized. The distance between the strongly basic lithium amide nitrogen atom and the abstracted β-hydrogen atom was 1.416 Å. The lithium atom is 1.819 Å from the epoxide oxygen atom to which it is coordinated. The epoxide O–C bond being broken has a length of 1.735 Å. A full frequency analysis was carried out to confirm that the optimized structure was a saddle point having only one imaginary frequency (ν=i 1407 cm^{-1}). An IRC[12] (Intrinsic Reaction Coordinate) calculation was also performed to make sure that the reactant system goes to the product system via this saddle point (TS), and vice versa. The reaction intermediate complex structure was constructed on the basis of these essential geometrical parameters as shown in Scheme 3. Then, these essential geometrical parameters are all fixed during the MM3 molecular mechanics calculations. In the process of determining the essential geometrical parameters, several other possible choices of fixed geometrical parameters were also considered, and the same MM analyses were carried out on these model systems. The best result was obtained when the geometrical parameters listed in Scheme 3 were adopted.

4. The most appropriate reaction intermediate complex model

There are check points when we select the most appropriate reaction intermediate complex model for the MM3 study on the enantioselectivity prediction after determining the essential geometrical parameters of the transition state (TS). The points to be checked are as follows.

(1) Should the lithium amide reagent be treated as a monomer, dimer, or trimer? What does the dimer look like?
(2) Should a solvent molecule (THF) be incorporated in the reaction intermediate complex?

Lithium amide compounds are well-known to exist as dimers or oligomers in solution by NMR experiments.[13] Therefore, the model where lithium amide is incorporated into the reaction intermediate complex as the dimeric form was also considered. However, the stabilization energy of the dimer due to the Lewis bonding interaction[14] between the Li and the N atoms was very large (~80 kcal/mol), and an appropriate reaction intermediate complex where the lithium amide dimer formed a suitable supra-molecule with cyclohexene oxide could not be found. Therefore, monomeric lithium amide was incorporated in the reaction intermediate complex. With



The Structure of the transition state composed of the $LiNH_2$ and propene oxide with MP2/6-31+G* ab initio calculations

The initial structure of the reaction intermediate complex model for chiral lithium amide B and cyclohexene oxide

$LiNH_2$ + propene oxide transition state

	(Å)
Li - N	1.882
Li···O	1.819
O - C	1.735
C - C	1.438
N···H	1.416

	(°)
N - Li···O	125.9
Li···O - C	107.2
O - C - C	117.5
C - C···N	106.4

	(*R*)-TS(°)
N - Li···O - C	-9.0
Li···O - C - C	21.4
O - C - C···N	-21.3
	(*S*)-TS(°)
N - Li···O - C	9.0
Li···O - C - C	-21.4
O - C - C···N	21.3

*Means that the position of the *-marked atoms was fixed in order to hold essential geometrical parameters (lengths, angles, dihedral angles shown in scheme) as those of the transition state

Scheme 3.

regard to the point how to deal with solvent molecule (THF) in the reaction intermediate complex, both models where THF is utilized or not were taken into account, and the MM3 calculations were carried out on the both models. Almost the same results with regard to the enantioselectivity prediction were obtained, so the more simple model (without THF) was adopted as an appropriate reaction intermediate complex. Note that the reaction intermediate complexes formed by substrate cyclohexene oxide and chiral lithium amide as shown in Figures 2 and 3, and the essential geometrical parameters inherent to the transition state of this asymmetric reaction are retained as fixed values during the MM3 calculations.

5. How to evaluate the enantioselectivity in the asymmetric synthesis of chiral 2-cyclohexen-1-ol by using MM3 calculations

The input data of the four types of reaction intermediate complexes labeled (*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2** as shown in Figure 3 for the MM3 calculations were made by expanding the structure constructed on the basis of the essential geometrical parameters for the transition state (TS). Stochastic conformational search[15] was carried out on each reaction intermediate by using the expanded the MM3 (2000) force field[16] which can deal with the lithium amide functional group, to exclusively locate possible energy minima at an ambient temperature. The essential geometrical parameters for the TS were kept constant during the MM3 calculations. The local minimum energy structures within a 3.0 kcal/mol energy range relative to the most stable reaction intermediate complex were found as stable existing reaction intermediate complexes at an ambient temperature. Though exhaustive conformational search was carried out on every reaction intermediate complex (**A**–**I**), the only one dominant conformer for each (*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2** type complex was actually found to exist. Conformational diversity could not be recognized. This may come from that the reaction intermediate complexes are rather rigid due to the strong Lewis bonding interaction[14] between the Li and the electronegative atoms such as nitrogen or oxygen. By using thus obtained conformational energies of (*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2** reaction intermediate complexes, the population of these complexes which can lead to the generation of the (*R*)-2-cyclohexen-1-ol or (*S*)-2-cyclohexen-1-ol was calculated. The calculated population values (MM3[% pop(*S*)] or MM3[% pop(*R*)]) were used as a parameter to correlate with the experimentally determined % ee values.

Table 1

Populations[a] of the reaction intermediate complexes containing chiral lithium amides **A**–**I** calculated by the MM3 force field

Lithium amide	(*R*)-Precursor		(*S*)-Precursor	
	Type 1	Type 2	Type 1	Type 2
A	0.0	0.4	0.0	99.6
B	11.0	12.0	0.1	76.9
C	9.6	34.1	0.2	56.1
D	11.4	25.0	0.2	63.4
E	10.0	29.3	0.2	60.5
F	0.0	98.9	0.0	1.1
G	8.5	40.6	0.1	50.8
H	1.3	11.0	0.0	87.7
I	26.4	0.1	0.0	73.5

[a] Population is expressed as % at 298 K.

6. Theoretically estimated enantioselectivity by using the MM3 force field

The population numbers of the reaction intermediate complexes ((*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2**) obtained from the exhaustive conformational survey by the MM3 force field calculations are summarized in Table 1. The MM3 force field predicts that chiral lithium amides **A**–**E** and **G**–**I** will show catalytic effect favorable to the production of (*S*)-2-cyclohexen-1-ol, while to the contrary, lithium amide **F** will exert (*R*)-form enantioselectivity. The MM3 calculations have revealed that the most stable conformer of each reaction intermediate complex containing lithium amides **A**–**I** is more stable than the other conformers by 2 kcal/mol. Therefore, more than 95% of the stable conformers of the **A**–**I** complexes take the most stable conformation. In order to check how well the MM3 calculations can predict the enantioselectivity, the summed up population values (MM3[% pop(*S*)] or MM3[% pop(*R*)]) for producing the (*S*)- or (*R*)-2-cyclohexen-1-ol were calculated, and the correlation between the calculated MM3[% pop(*S*)] and the experimentally determined % ee(*S*) was investigated. The result is shown in Figure 4. The correlation equation is expressed as Eq. 1.

$$\mathrm{Expt}[\%\,\mathrm{ee}(S)] = 0.55\,\mathrm{MM3}[\%\,\mathrm{pop}(S)] + 37.2 \quad R = 0.84 \qquad (1)$$

As a rather good linear correlation was observed, we can judge that the enantioselectivity for the asymmetric synthesis of chiral 2-cyclohexen-1-ol could be well evaluated by

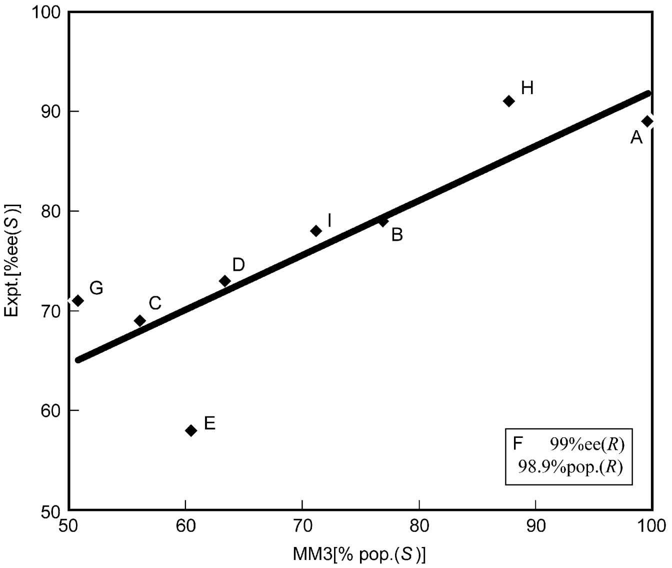
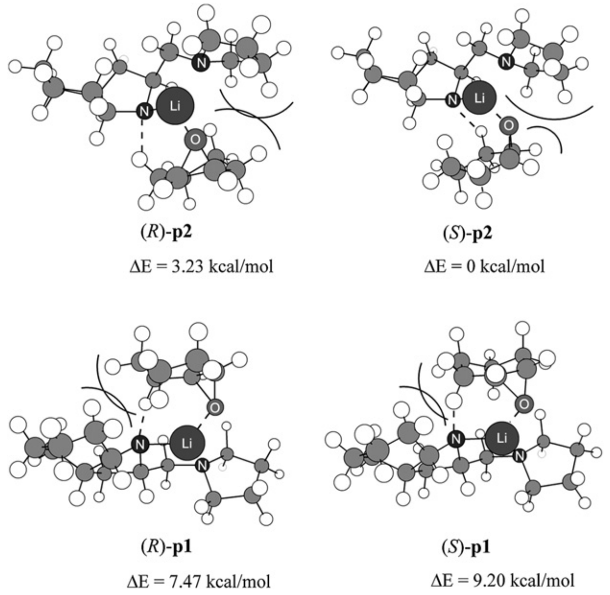


Figure 4. Correlation plot between the MM3 calculated populations of the reaction intermediate complexes (MM3[% pop(*S*)]) and the experimentally determined % ee (Expt[% ee(*S*)]).

calculating the conformational energies of the reaction intermediate complex models comprised of chiral lithium amides and cyclohexene oxide. It should be noted that a chiral lithium amide **F** (having (*R*)-configuration at the chiral carbon atom next to the lithium amide nitrogen) developed by Andersson's group[4] was correctly estimated to give rise to an (*R*)-enantioselectivity by this MM3 theoretical approach though (*R*)-enantioselectivity could not be estimated directly from the correlation plot in Figure 4. The chiral steric environment in the reaction intermediate complexes in this asymmetric synthesis is well reproduced by the MM3 force field.

Why does chiral lithium amide **A** show (*S*)-enantioselectivity? What kind of steric interactions are critical to exert enantioselectivity? To answer these questions, the optimized structures of the reaction intermediate complexes calculated by the MM3 force field were investigated in detail. As the population of the most stable conformation for the every reaction intermediate complex (**A**−**I**) is dominant (>95%, vide supra), the most stable conformations of each of four type reaction intermediate complexes ((*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2**) were considered to assess the structural interactions in the chiral environment. As an example, reaction intermediate complexes of lithium amide **A** were shown to compare the structural differences and their related structural interactions among the four type reaction intermediate complexes. The optimized geometries and their conformational energies are shown in Figure 5.

As shown in Figure 5, steric hindrance between the pyrrolidine ring attached at C2 of the lithium (*S*)-2-pyrrolidide and cyclohexene oxide ring in (*R*)-**p2** is evidently larger than the case of (*S*)-**p2** (ΔE=3.23 kcal/mol). In both of the (*R*)-**p1** and (*S*)-**p1** reaction intermediate complexes, rather larger repulsive interactions between the pyrrolidine and the cyclohexene oxide rings were also recognized. The MM3 results show that the repulsive van der Waals energies between the sterically adjacent hydrogen atoms on pyrrolidine and the cyclohexene oxide rings were approximately 0.5 kcal/mol (H···H) with a distance of ∼2.15 Å. If this non bonding (H···H) distance is shorter than 2.0 Å, rather big repulsive potential (>1 kcal/mol) will exert to destabilize the intermediate complex. These van der Waals interactions are assumed to be the main factor exerting enantioselectivity in the reaction intermediate complexes. The entropic contribution to the enantioselectivity should also be considered when we compare the experimental results with the theoretical ones. Significant entropy effect such as the rotational entropy exemplified by the number of possible conformations of pyrrolidine unit could not be actually recognized. This is partly because the reaction intermediate complexes containing the lithium amide are structurally rigid due to the strong Lewis bonding interactions (vide supra). Exact evaluation of the entropic contribution on these reaction intermediate complexes may be possible if the vibrational calculation could be carried out accurately. However, we cannot do that at the present stage because our model for the reaction intermediate complex is an approximate one where some geometrical parameters are fixed to reflect the characteristics intrinsic to the transition state. In the other reaction intermediate complexes containing chiral lithium amides **B**−**E** and **G**−**I**, similar steric repulsions between the pyrrolidine ring attached at C2 of the lithium (*S*)-2-pyrrolidide and cyclohexene oxide were evident in the reaction intermediate complexes of (*R*)-precursor. The optimized reaction intermediate structure of the (*S*)-**p2** is not only energetically favorable but also very suitable for the hydrogen abstraction step of the β-proton of the epoxide by the strongly basic lithium amide nitrogen atom. That is the reason why chiral lithium amide reagents **A**−**E** and **G**−**I** yield (*S*)-enantioselectivity. The stereochemical configuration of the chiral lithium amide **F** (having an inverse (*R*) chiral environment at the chiral carbon next to the lithium amide nitrogen) is contrarily different from those of **A**−**E** and **G**−**I** (having (*S*)-configuration). Compare the optimized geometries and their conformational energies for the chiral lithium amide **F** (Fig. 6) with those of the lithium amide **A**. In the case of the lithium amide **F**, (*R*)-**p2** conformer is the most stable because this intermediate structure can alleviate steric repulsions between the adjacent hydrogen atoms more effectively than those of the (*S*) type structures.



(*R*)-**p2**
ΔE = 3.23 kcal/mol

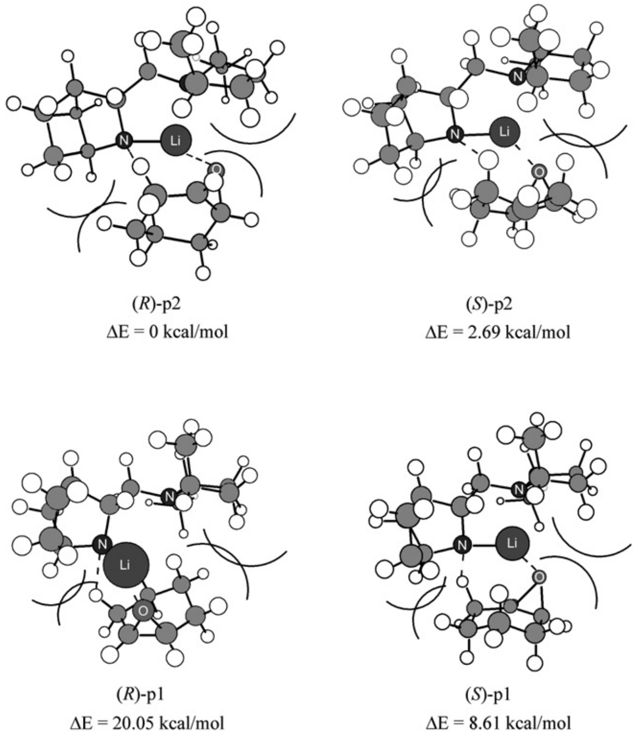
(*S*)-**p2**
ΔE = 0 kcal/mol

(*R*)-**p1**
ΔE = 7.47 kcal/mol

(*S*)-**p1**
ΔE = 9.20 kcal/mol

Figure 5. Optimized structures of the four type reaction intermediate complexes for chiral lithium amide **A** and their relative conformational energies (ΔE: kcal/mol).

As steric repulsion among the substituents attached on the chiral lithium amide and the cyclohexene oxide can be evaluated properly for the reaction intermediate complexes (*R*)-**p1**, (*S*)-**p1**, (*R*)-**p2**, and (*S*)-**p2** with our MM3 force field approach, enantioselective preference of a chiral lithium amide reagent in the asymmetric synthesis can be predicted well from the population numbers of the reaction intermediate complexes (MM3[% pop(*S*)] or MM3[% pop(*R*)]) leading to (*S*)- or (*R*)-2-cyclohexen-1-ol. A chiral lithium amide reagent which can produce a proper chiral environment in the reaction intermediate complex, where a rather big conformational energy difference (ΔE>2 kcal/mol) between (*S*)- and (*R*)-precursor reaction intermediate complexes exists, is assumed to



(*R*)-p2
ΔE = 0 kcal/mol

(*S*)-p2
ΔE = 2.69 kcal/mol

(*R*)-p1
ΔE = 20.05 kcal/mol

(*S*)-p1
ΔE = 8.61 kcal/mol

Figure 6. Optimized structures of the four type reaction intermediate complexes for chiral lithium amide **F** {(*R*)-enantioselectivity} and their relative conformational energies (Δ*E*: kcal/mol).

be a good chiral reagent with splendid enantioselectivity in the asymmetric synthesis. Molecular design of a chiral lithium amide reagent for asymmetric synthesis may be very convenient and efficient utilizing this theoretical approach with the aid of the MM3 force field. We are now in the process of synthesizing the chiral lithium amide reagents which were estimated to exert excellent enantioselectivities for preparing (*S*)- or (*R*)-2-cyclohexen-1-ol by this MM3 approach, and to determine the experimental enantioselectivities. The results will be reported soon.

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