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Computational Studies of Effective Asymmetric Alkylation Utilizing a Chiral Schiff Base Derived from 2-Hydroxy-3-Pinanone - Part 2 -

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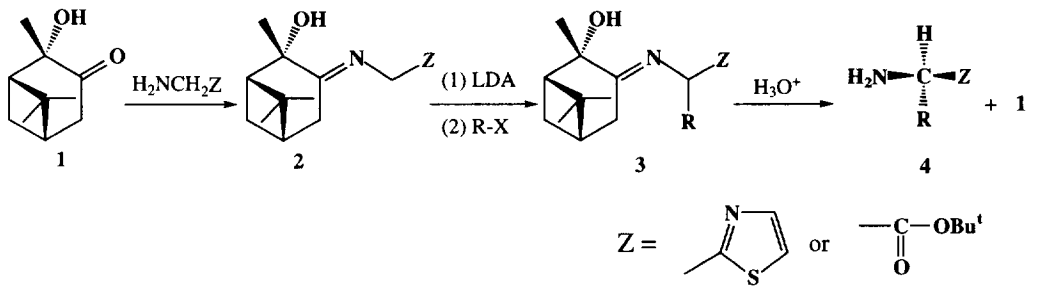
Abstract : Two proposed hypotheses concerning the mechanism of the effective asymmetric alkylation utilizing a chiral Schiff base derived from 2-hydroxy-3-pinanone **1** have been examined, including the influence of lithium and THF ligands.

In the preceding paper,[1] we reported a theoretical/computational investigation on the mechanism of the asymmetric alkylation utilizing the chiral Schiff base **2** (Z=2-thiazolyl) derived from 2-hydroxy-3-pinanone (**1**) and 2-thiazolylmethylamine.[2] We now report an analogous investigation on the mechanism of the asymmetric alkylation of the Schiff base **2** ($Z=CO_2Bu^t$) from 2-hydroxy-3-pinanone (**1**) and glycine tert-butyl ester,[3] outlined in Scheme 1.

Two research groups have proposed the mechanisms of the asymmetric alkylation. The hypothesis proposed by one of the authors (T. S.)[3] was that the asymmetric alkylation proceeded in a state of a monomeric cluster **5**, which was chiefly based on what had learned by experimental organic chemistry.



Scheme 1

The other one proposed by Solladié-Cavallo and co-workers[4,5] was that the asymmetric alkylation proceeded in a state of a dimeric cluster **6**, which was mainly based on a lot of information on enolates by X-ray crystallography. From their experimental results, they doubted whether the high stereoselectivity and the absolute configuration obtained could be explained by the steric effect or efficacy on the three-bond distance between the prochiral carbon undergoing the alkylation and the first chiral center in the case of a monomeric cluster **5**. To account for their experimental results, they proposed the mechanism of a dimeric cluster **6**, as shown in Figure 1.

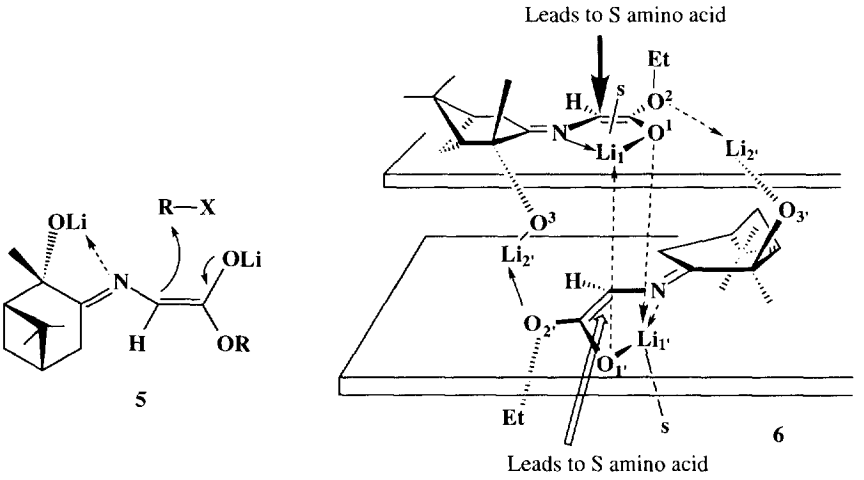


Figure 1 Proposed Asymmetric Alkylation Mechanism Models

In order to study this mechanism, the semi-empirical molecular orbital method, PM3 of MOPAC93,[6] was employed for all calculations using a HP Apollo DN10000 and a Titan 2-800 workstation. Input coordinates were built with the CSC Chem 3D Plus Ver. 3.1 on a Macintosh SE and a Power Macintosh 8100/80 personal computer. All calculations of compounds including lithium atom put to use the parameter of lithium which PM3 in MOPAC93 comprises.[7]

First we made a survey of the minimum energy structure of the chiral Schiff base of glycine ester, because we did not know its properties on the calculation except the experimental results. A structure of this chiral Schiff base was optimized with PM3. The geometry obtained was used as starting points for generation of 36×36 (1296) different conformations by stepwise rotation of 10 degrees around both important N12-C13 and C13-C14 bonds, and then they were optimized very well. Next the heat of fomation (ΔH_f) was calculated for all these conformations. A contour map was calculated in which ΔH_f was plotted as a function of two dihedral angls C6-N12-C13-C14 and N12-C13-C14-C15, respectively. The structures of local minimum and minimum energy conformations gained from the contour map were well reoptimized. As for the minimum energy structure of this Schiff base, the whole molecule looked like a rugby ball, shown in Figure 3. Moreover a hydrogen atom attacked by a base faced outside.

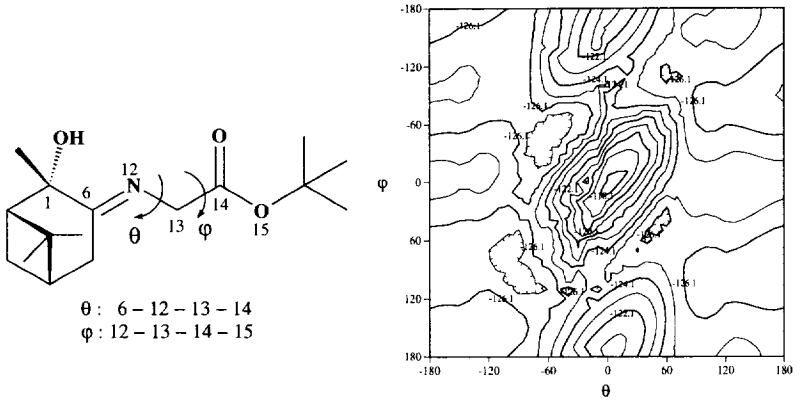
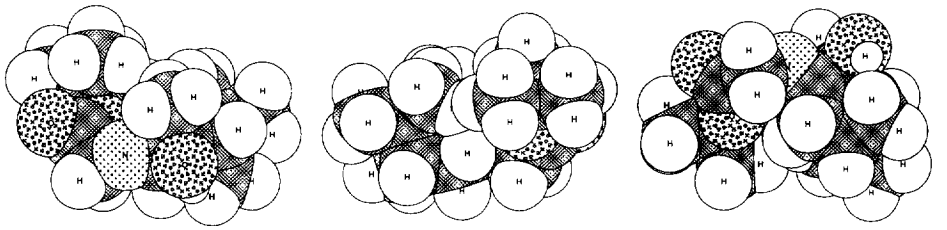


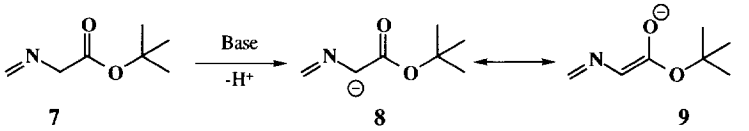
Figure 2

Table 1 Data of the *E*-Form Obtained from the Energy Surface

	θ / degrees	φ / degrees	ΔH_f /kcal•mol^{-1}
Max.	0	10	-117.6974
Min.	-100	70	-128.0677
Global Min.	-100.4	78.1	-128.1848

Figure 3 Global Minimum Optimized Structure of the *E*-Form





7 **8** **9**

Scheme 2

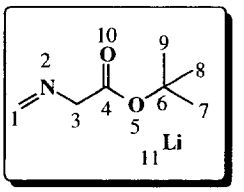


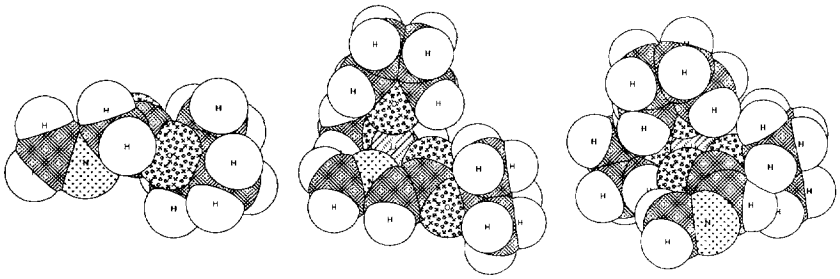
Figure 4 Atom Coordinate Number

Table 2 Net Atomic Charge with Li and THF Ligands

Coordinate Number	7	8	9
1	-0.0711	-0.3721	-0.2300
2	-0.1052	0.3444	0.0248
3	-0.0694	-0.6129	-0.4525
4	0.3918	0.4510	0.3550
5	-0.2615	-0.2369	-0.2137
6	0.1328	0.1324	0.1007
7	-0.1285	-0.1284	-0.1573
8	-0.1506	-0.1465	-0.1237
9	-0.1508	-0.1453	-0.1601
10	-0.3813	-0.4313	-0.4284
11		-0.0423	0.1074

Table 3 Charge with Li and THF using ESP[8]

Coordinate Number	7	8	9
1	0.0870	-0.5021	-0.0144
2	-0.4103	0.1924	-0.3664
3	0.1846	-0.6492	-0.1922
4	0.2396	0.2200	0.2512
5	-0.2673	-0.1756	-0.4741
6	0.3723	0.3109	0.5759
7	-0.2151	-0.0953	-0.3181
8	-0.4310	-0.1974	-0.2657
9	-0.2460	-0.2491	-0.4719
10	-0.3056	-0.3444	-0.4534
11		0.3429	0.6059



7 **8** **9**

Figure 5 Optimized Model Compounds

Table 4 ΔH_f of each model intermediate (kcal•mol^{-1})

	7	8	9
Without Li	-79.1751	-99.5259	-104.4025
With Li	———	-83.9670	-68.9583
With Li and THF ligands*	———	-203.6994	-190.1149

* As the number of THF ligands, **32**, **33** coordinated 2 molecules.

** ΔH_f of THF : -51.3902 kcal•mol^{-1}

Before a survey of the real system, we examined a model compound of the Schiff base of glycine to predict properties of the side chain.[7,9,10]

Calculations of the model compunds led to the following results. First, the base reacts at the carbon between the imino-nitrogen and the carbonyl function (Tables 2 and 3). This was in accord with the experimental results. Second, the coordinate number of lithium and THF as ligands were taken into consideration in case of the optimization. From these results, the effect of the reaction site which the alkylating reagents reacted with was not clear (Figure 5). Thus the prediction for properties of the side chain from these model compounds was completely hopeless. We supposed that this stereoselectivity could be explained from results of the real system.

Numerous organolithium compounds and lithium enolates were studied by Li or ^{1}H-NMR spectra and X-ray diffraction.[11,12] First, Weiss completed the infomation about the organolithium compounds.[13] The difference between structures in a solid state and ones in a solution state was especially worth of notice. For example, LiMe has the same strucutre between in a solid state and in a solution state. But LiBu^t has a tetramer in a solid state, while a dimer/monomer in a solution state. In other words, structures in a solution state are not always the same structures in a solid state. When a structure is big or complex, or includes solution molecules, it was difficult to make a higher dimensional cluster.

Table 5

In solution

Compound	Degree of association	Solvent
LiMe	tetramer	Et_2O, THF
LiEt	tetramer	Et_2O, THF
LiEt	hexamer	hydrocarbon
Li^{n}Bu	hexamer	hydrocarbon
Li^{n}Bu	tetramer / dimer	THF
Li^{t}Bu	tetramer	hydrocarbon
Li^{t}Bu	dimer / monomer	Et_2O, THF
LiPh	dimer	Et_2O, THF
$LiCH_2Ph$	>monomer	Et_2O, THF
LiC_3H_5	>monomer	Et_2O, THF

In crystal

Compound	Degree of association
$(LiMe)_4$	tetramer
$(LiEt)_4$	tetramer
$[Li(1\text{-norborny}l)]_4$	tetramer
$(Li^tBu)_4$	tetramer
$(Li^nBu)_6$	hexamer, cluster
$[Li(cyclohexyl)]_6$	hexamer, cluster
[Li(tetramethylcyclopropylmethyl)]$_6$	hexamer, cluster
$Li\{2,6\text{-}(NMe_2)_2C_6H_3\}]_3$	trimer, ring
$[Li(CH_2SiMe_3)]_6$	hexamer, ring
$[LiC(SiMe_3)_3]_2$	dimer

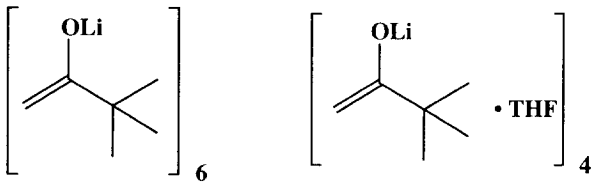
Base adducts

Componud	Degree of association
$[(LiMe)_4(tmeda)_2]_n$	3D net of tetramer
$[Li\{CH(SiMe_3)_2\}(pmdta)]$	monomer
$[Li^tBu(Et_2O)]_2$	dimer
$[Li(thf)_3][Li\{C(SiMe_3)_3\}_2]$	ion pair, ate complex
$[LiCH_2CH_2CH_2OMe]_4$	tetramer
$[LiCH_2CH_2CH_2NMe_2]_4$	tetramer
$[LiPh(Et_2O)]_4$	tetramer
$[LiPh(Me_2S)]_4$	tetramer
$[LiPh(tmeda)]_2$	dimer
[LiPh(pmdta)]	monomer
$[Li(2,4,6\text{-}^tBu_3C_6H_2)(tmpda)]$	monomer
$[LiC{\equiv}CH(en)]_n$	double chain (ladder stracture)
$[LiC{\equiv}CPh(tmpda)]_2$	dimer
$[(LiC{\equiv}CPh)_4(tmhda)_2]_n$	chain of tetramers (dobule helix)

Componud	Association
$[(LiC{\equiv}C^tBu)_4(thf)_4]$	tetramer
$[(LiC{\equiv}C^tBu)_{12}(thf)_4]$	stack
$[Li(allyl)(tmeda)]_n$	chain
$[Li(\eta^2\text{-allyl})(pmdta)]$	monomer
$[Li(\eta^3\text{-1,3-diphenylallyl})(Et_2O)]_n$	chain
$[Li\{\eta^3\text{-1,3-bis(trimethylsilyl)allyl}\}(tmeda)]$	monomer
$[Li(benzyl)(dabco)]_n$	chain
$[Li(benzyl)(Et_2O)]_4$	chain
[Li(benzyl)(tmeda)(thf)]	monomer
$[Li\{CH(SiMe_3)Ph\}(tmeda)]$	monomer
$[Li(CPh_3)(tmeda)]$	monomer
$[Li(CPh_3)(Et_2O)_2]$	monomer
$[Li(12\text{-crown-}4)_2][CHPh_2]$	ion pair
$[Li(12\text{-crown-}4)_2][CPh_3]$	ion pair

Abbreviations : tmeda= tetramethylenediamine, tmpda= tetramethyl-1,3-propylenediamine, tmhda= tetramethyl-1,6-hexylenediamine, pmdta= pentamethyldiethylenetriamine, dabco= 1,4-diazabicyclo[2.2.2]octane.

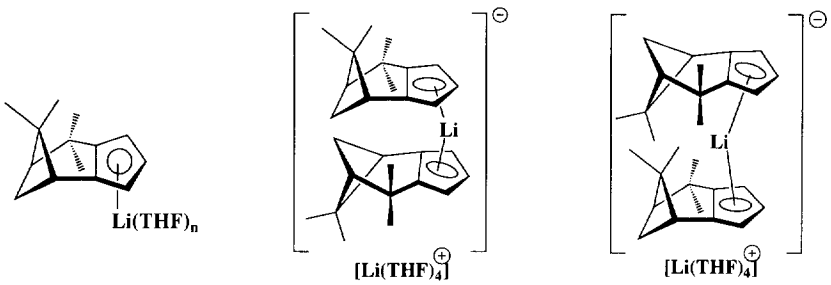
Second, Seebach reported the information about lithium enolates by X-ray diffraction.[14] A simple lithium enolate formed a hexamer **10** without solution molecules, and did a tetramer **11** with solution molecules (Figure 6). The case of enolates seemed also similar to one of organolithium compounds.



10 **11**

Figure 6

Third, forming the cluster of organolithium compounds depends on temperature.[12j] For instance, as for a verbenone-derivatized cyclopentadienyl compound, it was almost in a monomeric cluster at room temperature. But the state mixed a monomeric cluster **12** and dimeric clusters **13** and **14** at -80°C was observed . In other words, reduction of temperature to -80°C was required to form dimeric clusters (Figure 7 and Table 6).



12 **13** **14**

Figure 7

Table 6 Ratio of Each Structures

Ratio of **12 : 13 : 14**	Temp. (°C)	
57 : 31 : 11	-80	observed in THF-d_8
100 : 0 : 0	26	observed in THF-d_8
94 : 6	25	From variable-temperature NMR **12** : (**13**+**14**) =monomer : dimer

Thus it will be very important that structure in a solid state and in a solution is not always the same, and that forming a cluster depends on temperature. We doubted that the proposed high dimensional cluster **6** had the factor to control the stereoselectivity in solution. However, we could not deny the existence of the high dimensional cluster in solution in consideration of experimental conditions. When we thought the proposed intermediate models for asymmetric alkylation again, interpretation of this phenomenon was resonable for the monomeric cluster model **5**. On the other hand, the dimeric cluster

model **6** probably had some problems on this reaction. After an alkylating agent reacted on an enolate, we wonder how the other enolate reacted to control the stereoselectivity. After an alkylating agent reacted, there was no necessity of the ionic bond between the oxygen of the carbonyl function and lithium. Because a reaction product destroyed the dimeric cluster, the unreacted enolate might result in reducing the stereoselectivity. It was probably that the dimeric cluster model contradicted the explanation for the high stetreoselectivity of the asymmetric alkylation utilizing the chiral Schiff base.

Figure 8 Optimized Structures of Intermediate Clusters

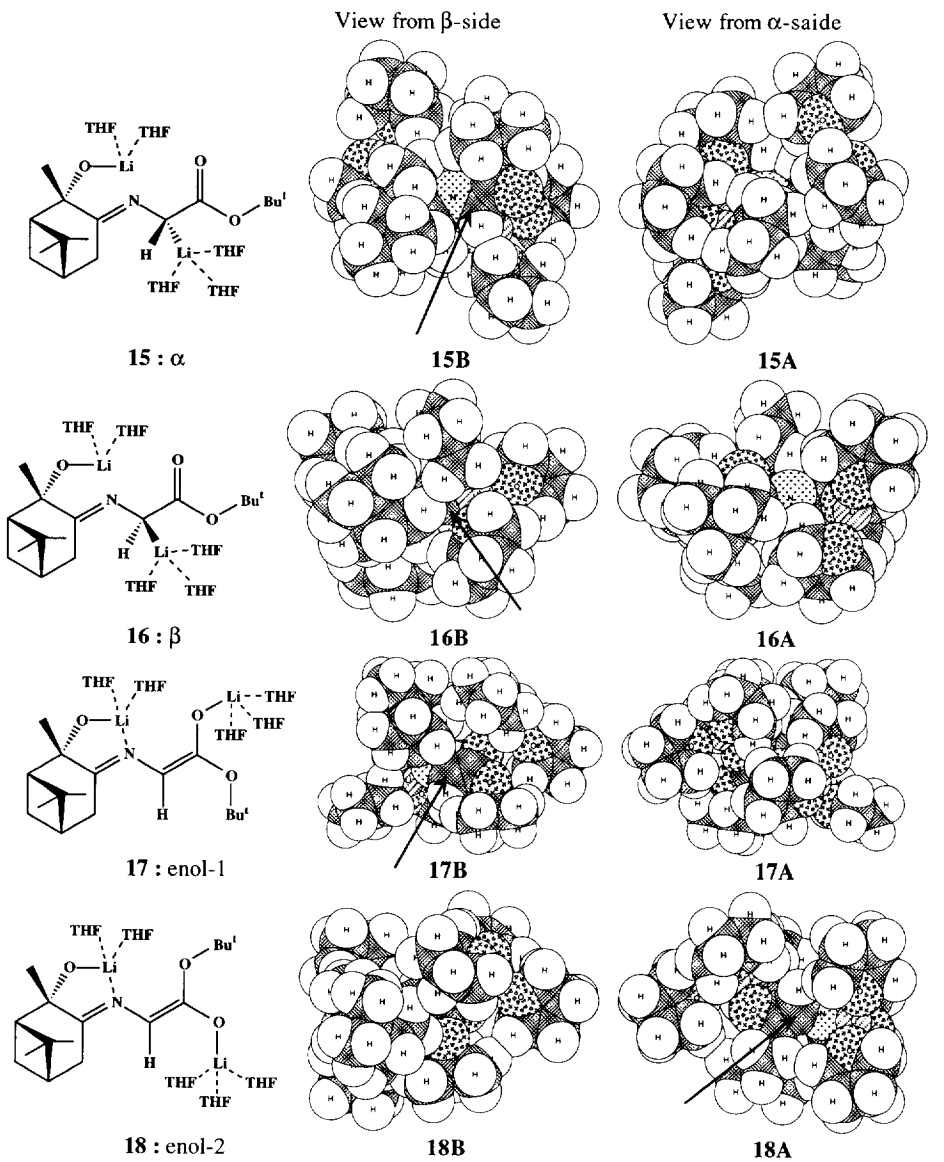
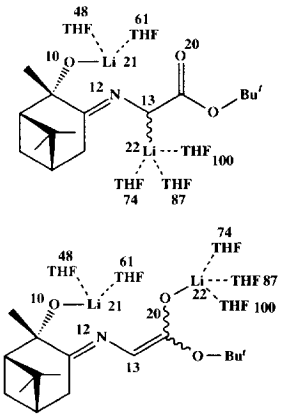


Table ΔH_f of each intermediate cluster (kcal•mol^{-1})

	15 : α	**16** : β	**17** : enol-1	**18** : enol-2
ΔH_f	-383.2980	-378.9798	-407.3003	-399.4882

Table 7 Bond Order of Intermediate Clusters

Atom Pairs		**15** : α	**16** : β	**17** : enol-1	**18** : enol-2
Li21	O10	0.8321	0.8738	0.6458	0.6651
	N12	0.0160	0.0083	0.4704	0.4743
	O48	0.2703	0.2725	0.2823	0.2833
	O61	0.2631	0.2643	0.2767	0.2722
Li22	C13	0.5940	0.5861	0.0255	0.0174
	O20	0.0137	0.0185	0.5834	0.5567
	O74	0.2773	0.2805	0.2644	0.2720
	O87	0.2932	0.2809	0.2599	0.2648
	O100	0.2767	0.2837	0.2677	0.2754



We ascertained wheher it was necessary to modify this presumption. The result taking account of a lot of information was that the proper structure for the asymmetric alkylation were **15** and **17** in case of the monomeric cluster model **5**. As for **16**, there were no reaction sites on both side for the main influence of lithium and THF ligands. As for **15**, there was no reaction site on the α-side for the effect of lithium and THF ligands. On the other hand, the β-side had the reaction site for the asymmetric alkylation. From the viewpoint of the heat of formation (ΔH_f), **15** was more stable than **16**. In the case of **17**, there was the reaction site on the β-side for the alkylation. This site was larger than the one of **15**. The α-side had no reaction site because of the lithium and THF ligands. In the case of **18**, there was the reaction site as a pocket on the α-side. However, THF molecules before the reaction site prevented an alkylating agent from approaching. Further more, ΔH_f of **17** was 7.81 kcal•mol^{-1} stabler than the one of **18**. From the bond order, **18** had the coordinate bond between the lithium and the nitrogen of the Schiff base. This is in accord with the hypothesis proposed by one of the authors (T. S.).[3] However, **15** did not have the coordinate bond between the lithium and the nitrogen. We thought the cause that a part of a THF molecule was wedged between the lithium and the nitrogen.

We further investigated the hypothesis proposed by Solladié-Cavallo and co-workers.[4,5] The dimeric cluster model **6** proposed by them was too complex to optimize the real system.[4,5] We made use of the model compound **19** which was modified to hold the character of the dimeric cluster model **6** (Figure 9). We assumed that this model compound **16** might have the stereoselective reaction site as the real dimeric cluster model **6** that the alkylating agents discriminated. Through trial and error we succeeded in making an initial input structure **20** of the model compound **19**. The initial strucutre **20** was optimized very well to give the structure **21**. Compared with before and after optimization of the model compound, **20** appeared to take down shells before optimization. On the other hand, **21** did to take up

shells after optimization. From these results, the optimized model structure **21** did not have the stereoselective reaction site which alkylating agents discriminated. In other words, the modified dimeric cluster model **19** did not have the specific reaction site (Figure 10). There was a conflict between the proposed hypothesis of the dimeric cluster model **6** and the calculated results. We think it is wrong to suppose that the dimeric cluster model **6** has the specific reaction site which alkylating agents discriminates. The cause was that the proposed dimeric cluster model **6** had a 4-membered ring structure with the coordinate bonds between the lithium and the nitrogen and between the lithium and the oxygen. We think that these bonds are too weak to maintain the 4-membered ring structure in the proposed model.

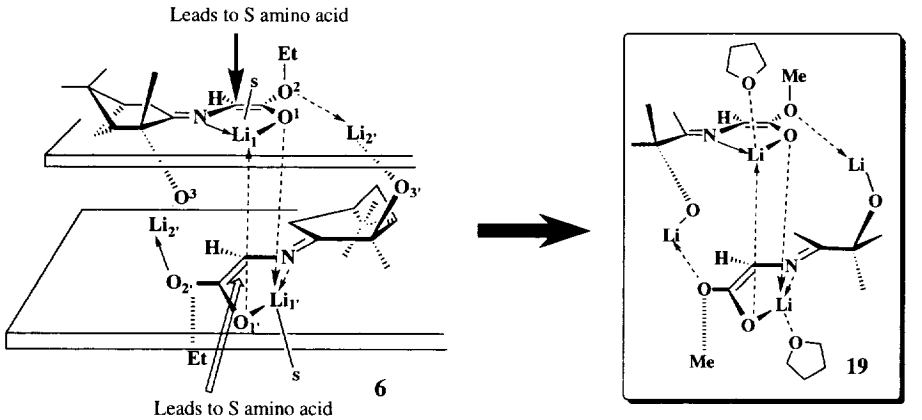
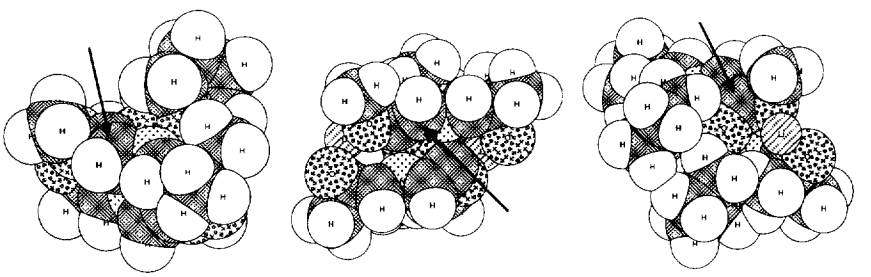


Figure 9

Before optimization : **20**



After Optimizaiton : **21**

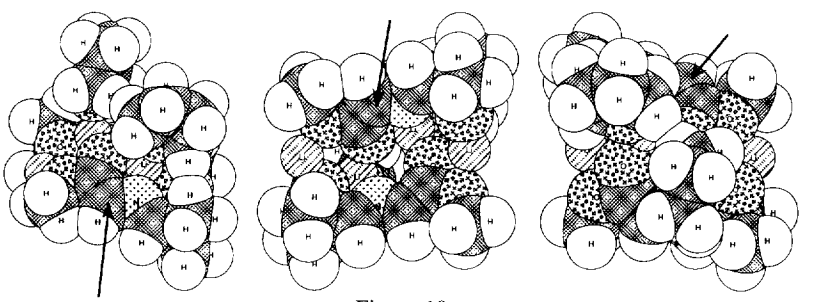
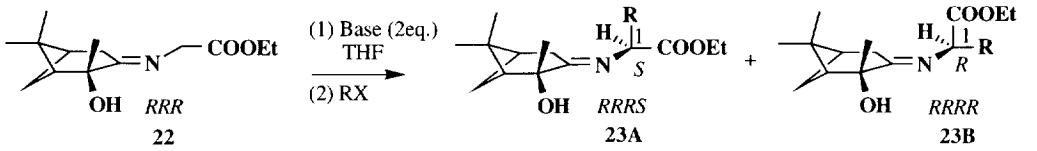


Figure 10



Base : LDA, ^{t}BuOLi, ^{t}BuOK, LDA+$MgBr_2$ (0.5eq.)
LDA+TBAF, ^{t}BuLi+$MgBr_2$ (0.5eq.), ^{t}BuOK+$MgBr_2$ (0.5eq.)
RX : MeI, $PhCH_2Br_2$

Scheme 3 Alkylation of Imino Ester **22** with MeI and $PhCH_2Br$

Solladié-Cavallo and co-workers made many experiments under various reaction conditions (Scheme 3),[4,5] and then they affirmed that the dimeric cluster model **6** had been able to fully rationalize the following results ; (a) the S configuration (S diastereoselectivity) obtained at C1 upon alkylation with alkyl halides, (b) the decrease in diastereoselectivity when the temperature increased, (c) the increase in S diastereoselectivity upon addition of $MgBr_2$ into the enolates before alkylation (thus reinforcing the folding and favoring the outer approach), and (d) the decrease in diastereoselectivity upon addition of tetra-n-butylammonium fluoride (TBAF) into the enolates before alkylation (thus disrupting the dimeric cluster and lowering the face differentiation). It is thus reasonable to postulate that this dimeric cluster model is more than the monomeric cluster model and that aggregates of this type might well be involved as reacting species. Therefore, the diastereoselectivity could be due but indirectry to the chiral auxiliary, the main origin of the diastereoselectivity being the self-clustering of the polyfunctionalized three-dimensional anion enolate, probaly favored by the rigidity of the bifunctionalized chiral fragment.

However, we have pointed out the contradictory parts of the dimeric cluster model **6** from our computed results. The monomeric cluster model **5** on this asymmetric alkylation mechanism proposed by one of the authors (T. S.)[3] has been able to comprehensively rationalize the experiments obtained by Solladié-Cavallo and co-workers. When lithium was changed into potassium, the difference of the ionic radius between lithium and potassium affected the rigid degree of making the cluster. We supposed that the cluster with potassium was not more rigid than the one with lithium. As regards the addition of TBAF into the reaction system, the structure of the cluster drastically changed because tetrabutylammonium ion contacted to the β-side. Thus we considered that an alkylating agent could attack from the α-side. For the addition of magnesium bromide into the reaction system, we imagined that the benefit of the addition was the function as the Lewis acid catalyst, judging from the solubility of magnesium bromide.[15] The equivalents of magnesium bromide in THF solution are out of accord with the ones which was added into the reaction system according to the hypothesis proposed by Solladié-Cavallo and co-workers.[4,5] Regarding this effect, the coordinate of the Lewis acid brought about the descent of the orbital energy, reinforcement of the orbital interaction, and the increase in the selectivity of the reaction site.

In conclusion, the asymmetric alkylation utilizing the chiral Schiff base was comprehensively clarified by the mechanism of the monomeric cluster model **5**.[1,2,3]

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15. Although there was no data of solubility for magnesium bromide in THF solution, data of solubility in diethyl ether solution was reported. We estimated the used volume of the solvent at 5 ml, and calculated the volume of $MgBr_2$ at -20°C. The soluble one was 4.41×10^{-2} mmol. We assumed that the solubility of $MgBr_2$ in THF solution was below this value. We judged that $MgBr_2$ functioned as the Lewis acid catalyst in the reaction system.

Table $MgBr_2$ - Et_2O System[a]

Solubility / wt.%	t / °C	Solubility / wt.%	t / °C
0.22	-20	1.81	16
0.40	-10	2.10	18
0.70	0	2.44	20
1.17	10	2.83	22
1.55	14		

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