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Computational Studies of Effective Asymmetric Alkylation Utilizing a Chiral Schiff Base Derived from 2-Hydroxy-3-Pinanone - Part 1 -

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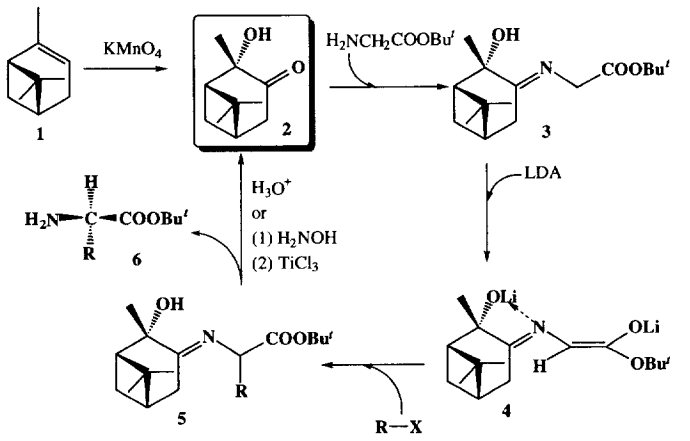
Abstract *:* The calculation by the semi-empirical molecular orbital method concerning the mechanism of the effective asymmetric alkylation utilizing a chiral Schiff base derived from 2-hydroxy-3-pinanone (**2**) has revealed that the factor which controls the stereoselectivity is mainly the influence of the lithium and THF ligands. The result has demonstrated the proposed hypothesis which is based on many experiments.

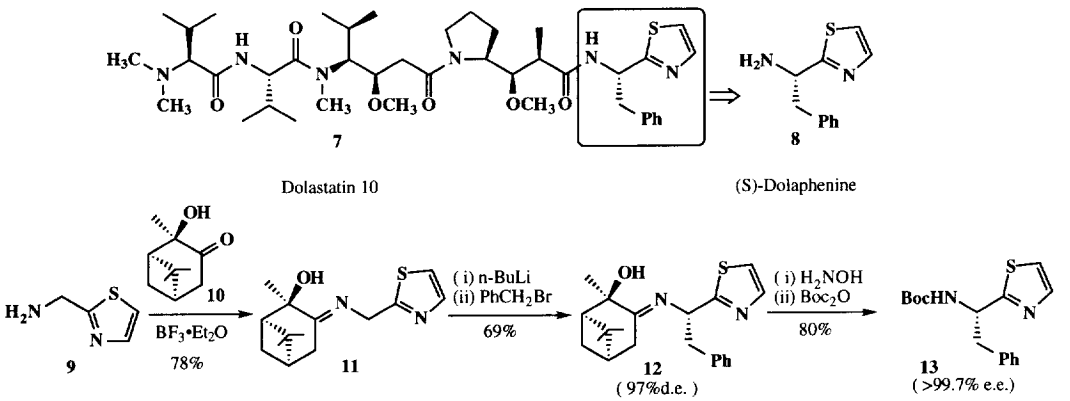
In 1976, an effective asymmetric alkylation was developed by utilizing a chiral Schiff base of glycine ester derived from (-)-2-hydroxy-3-pinanone **2**.[1] As shown in Scheme 1, (-)-2-hydroxy-3-pinanone (**2**) easily available from α-pinene (**1**) is condensed with glycine tert-butyl ester to give the Schiff base **3**. Lithiation of **4** followed by alkylation affords the alkylated Schiff base **5** from which the chiral auxiliary **2** is easily removed by acidic hydrolysis or oximation followed by treatment with $TiCl_3$. The resulting α-amino acid tert-butyl esters **6** show high optical purity. This method has four advantages over known various asymmetric syntheses ; (1) good optical and chemical yield, (2) recycle of the chiral reagents, (3) experimental simplicity, and (4) commercial availability of both antipodes of α-pinene (**1**) in nature as well as those of 2-hydroxy-3-pinanone (**2**).

This asymmetric alkylation method has been efficiently applied to the preparation of optically active α-amino acids, amines, and α-aminophosphonic acids.[2b] Utilizing this method, we have recently succeeded in an efficient synthesis of (S)-dolaphenine (**8**), the C-terminal unit of a strong antitumor marine natural product dolastatin 10 (**7**), as its tert-butyloxycarbonyl(Boc) derivative **13**,[2] as shown in Scheme 2.

Although this method is quite efficient, the mechanism of the asymmetric alkylation has not been elucidated in detail yet. There are no fundamental data to support the asymmetric alkylation mechanism except a proposed hypothesis.[1] We now report a theoretical/computational investigation on the mechanism of asymmetric alkylation utilizing the chiral Schiff base in order to clarify the factors that control the stereoselectivity.



Scheme 1 Amino Acid Asymmetric Synthesis Cycle



Scheme 2 Synthesis of (S)-Dolaphenine

In order to study this mechanism, the semi-empirical molecular orbital method, PM3 of MOPAC93,[3] 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.[4]

First we considered whether the stereostructure of the chiral Schiff base was correct from the viewpoint of the minimum energetic structure. Since the preparation of the chiral Schiff base was carried out by reflux, the stereostructure of the chiral Schiff base will depend on thermodynamic stability. The global minimum energy of the chiral Schiff base with the thiazole function was searched in order to prove the proposed hypothesis. The structure of the chiral Schiff base with the thiazole function was optimized with PM3. Thus the geometry obtained was used as starting points for the generation of 72×72 (5184) different conformations by stepwise rotation of 5 degrees around both N12-C13 and C13-C14 bonds, and

then they were optimized very well. Next the heat of formation (ΔH_f) was calculated for all these conformations. A contour map was calculated in which the ΔH_f was plotted as a function of the two dihedral angles C6-N12-C13-C14 and N12-C13-C14-N15, respectively. The structures of local minimum and minimum energy conformations gained from the contour map were reoptimized well.

From the energy surface of the *E*-form, there are large domains which can be thermodynamically stable (Figure 1). Besides, from one of the *Z*-form, there are some thermodynamically stable areas which are more stable than the *E*-form (Figure 3). After all, we did not identify the stereoisomer of the chiral Schiff base from thermodynamic stability of each geometric structures.

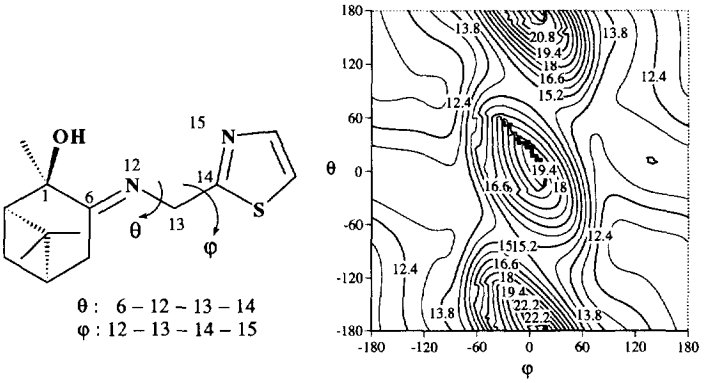
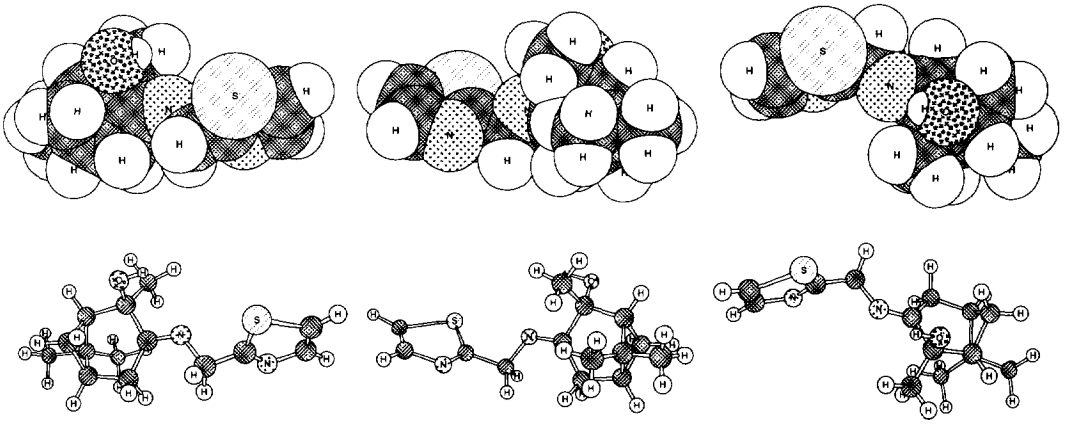


Figure 1

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

	θ / degrees	φ / degrees	ΔH_f /kcal•mol^{-1}
Max.	10	-165	23.6524
Min.	165	-105	11.4022
Global Min.	164.7	-104.7	11.4021

Figure 2 Global Minimum Optimized Structure of *E*-Form



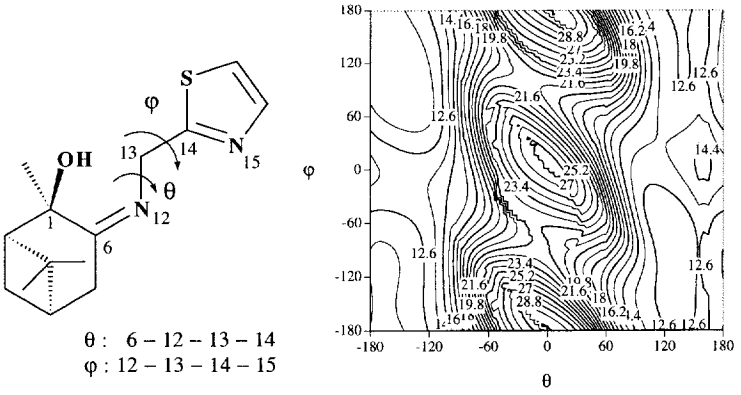
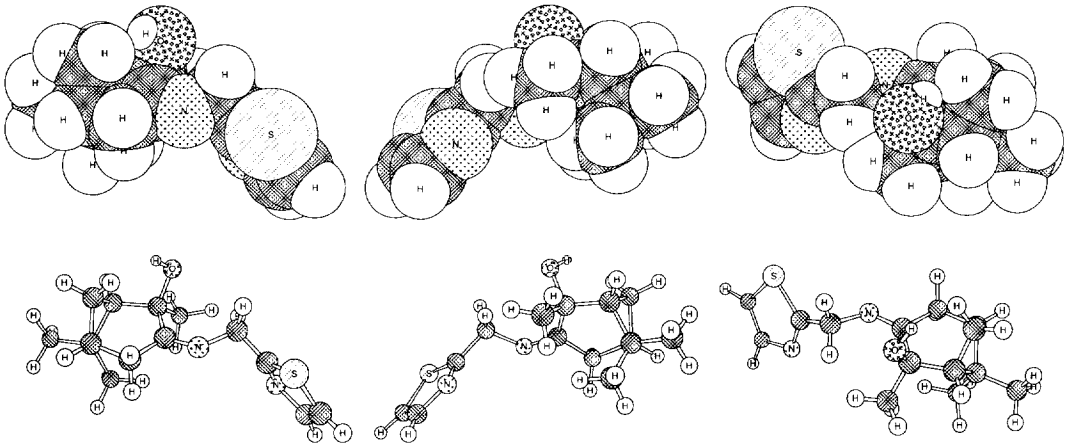


Figure 3

Table 2 Data of Z-Form Obtained from the Energy Surface

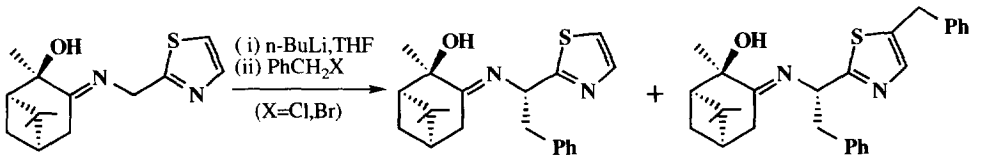
	θ / degrees	φ / degrees	ΔH_f /kcal•mol^{-1}
Max.	0	180	30.7108
Min.	-145	90	10.8855
Global Min.	-144.9	89.7	10.8855

Figure 4 Global Minimum Optimized Structure of Z-Form



Some experiments made it clear that the dialkylation occured under some reaction conditions (Table 3)[2]. We thought that the detailed analysis of structures and charge distributions might resolve this problem (Scheme 3).[4~8] Before the survey of the real system, we examined the model compounds **17**, **18**, and **19** for the chiral Schiff base having the thiazole function to predict properties of the side chain. Another aim was the search for the overalkylation in the case of the thiazole function.

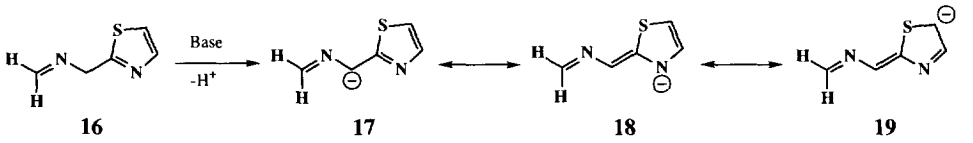
Table 3



12 14 15

Run	X	Reaction Conditions		Monobenzylated : 14		Dibenzylated : 15		Recovery of the Schiff Base (%)
				Yield(%)	de(%)[a]	Yield(%)	de(%)[a]	
1	Cl	−78°C :	6h	46	97	0	—	33
2	Cl	0°C :	1h	52	97	3	87	0
3	Br	−78°C :	2h	69	97	3	82	0
4	Br	0°C :	0.5h	47	97	27	89	0

(a) Determined by ^{1}H-NMR spectral analysis



16 17 18 19

Scheme 3

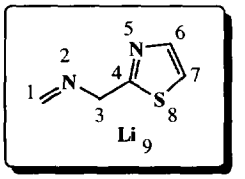


Figure 5 Atom Coordinate Number

Table 4 Net Atomic Charge with Li anf THF ligands

Coordinate Number	16	17	18	19
1	-0.0686	-0.4097	-0.3082	-0.1239
2	-0.1147	0.3264	0.3090	-0.0180
3	0.0107	-0.5122	-0.4629	-0.1750
4	-0.2120	0.0148	-0.0590	-0.2231
5	-0.0660	-0.2449	-0.0735	0.0072
6	-0.1031	-0.0217	-0.0822	-0.0292
7	-0.3357	-0.4434	-0.4184	-0.4295
8	0.3092	0.1753	0.2093	0.0613
9		0.0011	-0.1175	-0.1140

Table 5 Charge with Li using ESP Method[9]

Coordinate Number	16	17	18	19
1	0.1497	-0.6727	-0.4847	0.0318
2	-0.4082	0.5333	0.3068	-0.3439
3	0.0169	-0.9746	-0.6356	-0.0949
4	0.0856	0.4428	-0.0101	0.0172
5	-0.2662	-0.5366	-0.0286	-0.3422
6	-0.0737	0.1659	-0.3046	0.0557
7	-0.3814	-0.6336	-0.4269	-0.1344
8	0.1346	0.0022	0.0880	-0.3120
9		0.2113	0.1708	0.0307

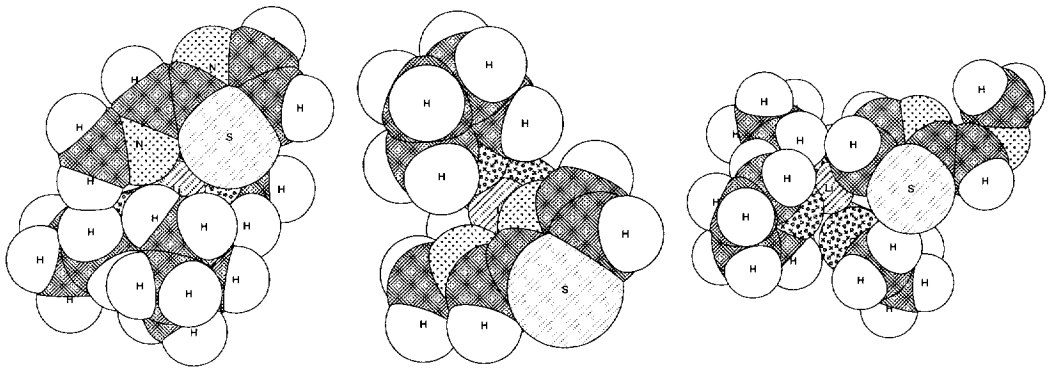


Figure 6 Optimized Model Compounds

Table 7 ΔH_f of Each Model Intermediate (kcal•mol^{-1})

	16	**17**	**18**	**19**
Without Li	61.2383	30.5623	32.2406	29.8519
With Li	———	71.4024	48.2831	83.0641
With Li and THF ligands*	———	-98.9420	-72.6852	-109.2838

* As the numbers of THF ligands, **17**, **19** coordinated 3 molecules, and **18** did 2 molecules

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

Calculations of the model compounds led to the following two results. First, the base reacts at the carbon between the imino-nitrogen and the thiazole ring. This was in accord with the experimental results. After the base was replaced with the hydrogen atom, the negative charge was transferred from the carbon atom between the imino nitrogen and the aromatic ring to the carbon atom next to the sulfur atom of the thiazole function (**17**→**19**, Scheme 3). Then the first step of the alkylation started at the thiazole ring. If the alkylation order were opposite, this reaction would be equal to the monoalkylation. In short, alkylating agents did not first react on the thiazole ring. Second, the coordinate number of lithium and THF as ligands were taken into consideration in the case of the optimization. From these results, THF as ligands would afford not a little the reaction site which the alkylating reagents reacted with. We presumed that THF as ligands would remarkably influence the reaction site in the actual system **12** like the model system.

Therefore the calculations were carried out in which the coordinate number of the lithium, THF as ligands, and the results of the model system were taken into consideration. The thiazole function was replaced with the phenyl one because of the size and complexity of the actual system.

We thought some structures from which the chiral center contacted the lithium and the geometrical isomer of the Schiff base were different.[4~8] They were optimized very well, as shown in Figure 7.

Figure 7 Optimized Structures of Intermediate Clusters

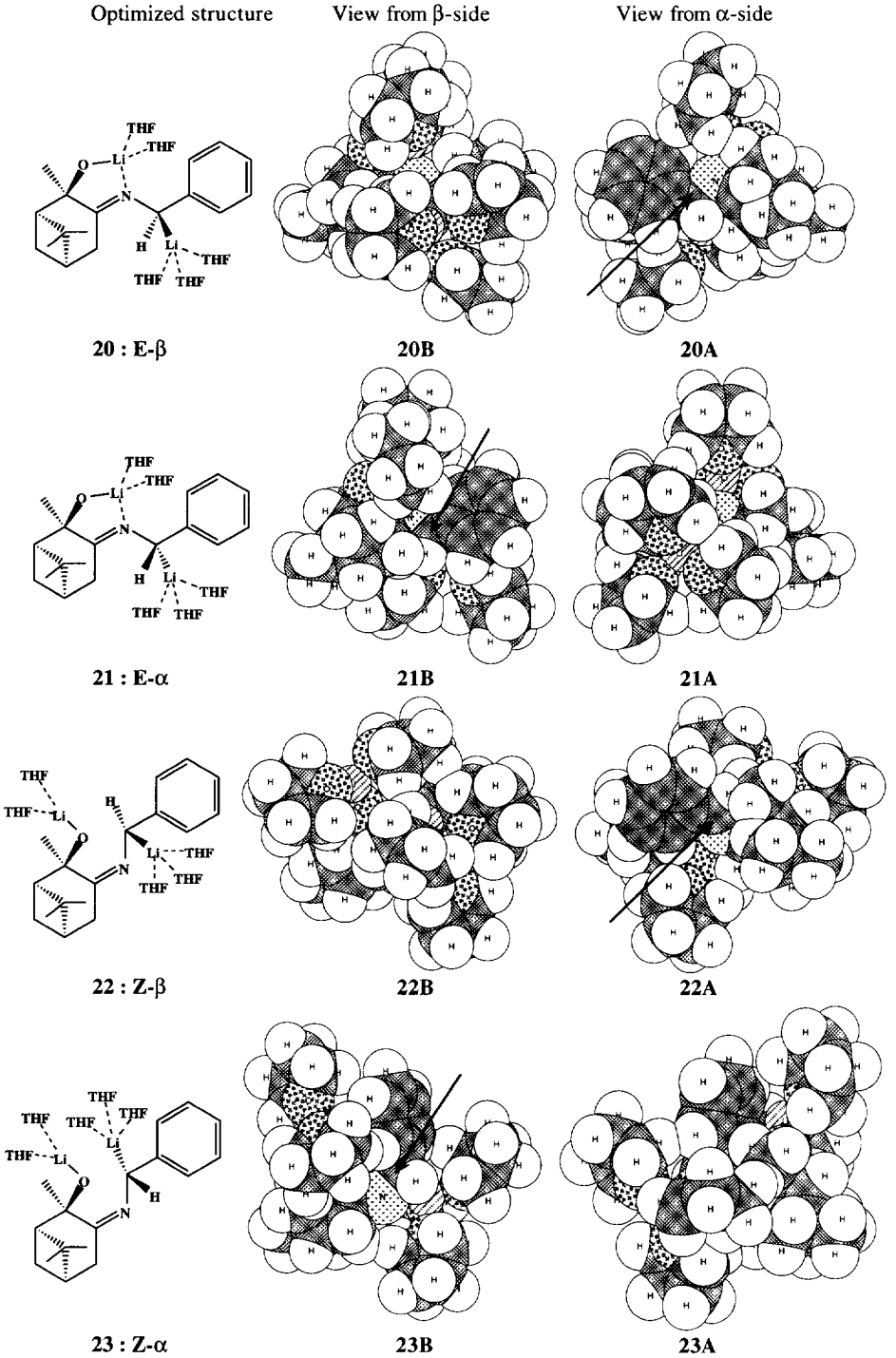


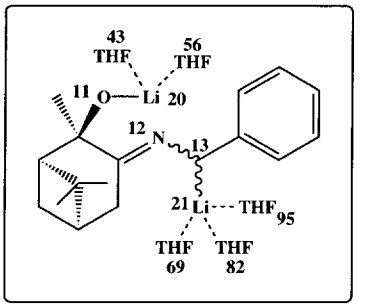
Table 8 ΔH_f of Each Intermediate Cluster (kcal•mol^{-1})

	E	*Z*
α	-264.2482	-252.8174
β	-263.6823	-261.2478

Table 9 Bond Order of Intermediate Clusters

Atom Pairs		**20** : *E*-β	**21**: *E*-α	**22** : *Z*-β	**23** : *Z*-α
Li20	O11	0.6539	0.6526	0.8597	0.8089
	N12	0.4783	0.4529	0.0044	0.0049
	O43	0.2708	0.2621	0.2661	0.2531
	O56	0.2588	0.2725	0.2780	0.2592
Li21	C13	0.5513	0.5681	0.1466*	0.6441
	O69	0.2878	0.2816	0.2552	0.2802
	O82	0.2734	0.2882	0.2469	0.2684
	O95	0.2889	0.2852	0.2290	0.2803

* Li21 - N12 : 0.4728



From these results, the structure **20** which could produce a new chiral center had the *E*-form of the Schiff base and the β-side contacted lithium, when the chiral Schiff base reacted with an alkylating agent.[8] In the case of **21**, there were no reaction sites for the effect of lithium-THF ligands. On the other side, there were few reaction sites because of the existence of the hydrogen atom. In the case of **22**, there were no reaction sites for the influence of the lithium-THF ligands and the existence of the hydrogen atom. On the other side, this configuration remained the small reaction site possibly to attack some alkylating agents which had small molecular volume. But the ΔH_f of this configuration was the highest than the other structures, shown in Table 8. We considered that this did not exist in the actual reaction system. In the case of **23**, there were also no reaction sites attached by an alkylating agent.

From the standpoint of heat of formation for the *E*-form, the difference between the α-side and the β-side was 0.566 kcal•mol^{-1}. To take account of the chemical equilibrium, though the equilibrium somewhat inclined to the α-side, it moved from the α-side to the β-side to react with an alkylating agent.

For the bond order of **20**, the coordinate bond between lithium contacting a spot of the previous third alcohol and the nitrogen atom of the Schiff base bonded obviously (Table 9). This was in agreement on the proposed hypothesis.[1,2] In consequence of a series of the investigation, a new chiral center will be produced due to the limitation of the reaction site to react on alkylating agents by the cluster of the lithium-THF ligands.

In conclusion, the following points will be considered for the asymmetric alkylation utilizing the this chiral Schiff base from the viewpoint of molecular design.

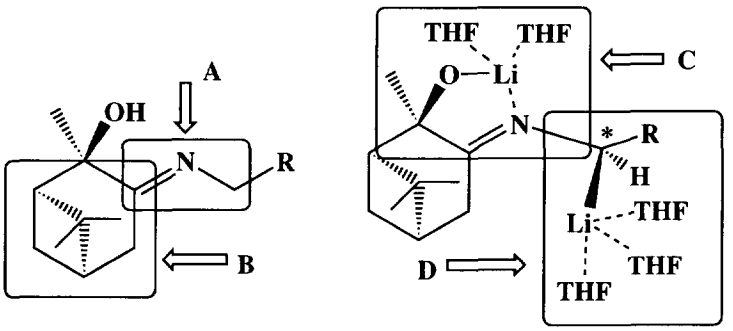


Figure 8

Domain A The structure of the Schiff base is the E-form because of thermodynamic stability.

Domain B Bridge parts have better exist inside the 6-membered ring rather than outside to be a rigid fragment.

Domain C The coordinate bond between Li and N is made, and a new 5-membered ring is formed. This domain supports the stereoselectivity of alkylation.

Domain D This domain deeply relates to the stereoselectivity of alkylation, which reacts with alkylating agents in cooperation with indirect steric effect of domain C.

The computational studies of the asymmetric alkylation shown in Scheme 1 will be the subject of the following paper.[10]

REFERENCES AND NOTES

1. (a) Yamada, S.; Oguri, T.; Shioiri, T. *J. Chem. Soc. Chem. Commun.*, **1976**, 136., (b) Oguri, T.; Kawai, N.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.*, **1978**, *26*, 803.
2. (a) Irako, N.; Hamada, Y.; Shioiri, T. *Presented in part at the 113th Annual Meeting of the Pharmaceutical Society of Japan,* Osaka, March, **1993**, *Abstracts of Papers 2*, 135., (b) Irako, N.; Hamada, Y.; Shioiri, T. *Tetrahedron*, **1995**, *51*, 12731 and references therein.
3. MOPAC 93.00, Stewart, J. J. P., Fujitsu Ltd., Tokyo, Japan, **1993**. Available from Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN.
4. Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.*, **1993**, *14*, 1301.
5. (a) *CA Index Guide, Appendix IV*, **1992**, P202-203., (b) International Union of Pure and Applied Chemistry, *Nomenclature of Organic Chemistry, Section A, B, C, D, E, F, and H, 1979ed.*, Pergmon Press, Oxford (England) **1979,** Section E and Appendix 2, P473-490.

6. (a) Jemmis, E. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.*, **1982,** *104*, 4781., (b) Neugebauer, W.; Clark, T.; Schleyer, P. v. R. *Chem. Ber.*, **1983**, *116*, 3282., (c) Jiao, H.; Schleyer, P. v. R. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1760., (d) Jiao, H.; Schleyer, P. v. R. *J. Chem Soc. Faraday Trans.*, **1994**, *90*, 1559.
7. (a) Neugebauer, W.; Kos, A. J.; Schleyer, P. v. R. *J. Organomet. Chem.*, **1982**, *228*, 107., (b) Wilhelm, D.; Clark, T.; Schleyer, P. v. R. *J. Chem. Soc. Chem. Commun.*, **1983**, 211., (c) Wilhelm, D.; Clark, T.; Schleyer, P.v. R.; Courtneidge, J. L.; Davies, A. G. *J. Am. Chem. Soc.*, **1984**, *106*, 361., (d) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Ared, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.*, **1984**, *106*, 6467.
8. (a) Paquette, L. A.; Bauer, W.; Sivik, M. R.; Bühl, M.; Feigel, M.; Schleyer, P. v. R. *J. Am. Chem.Soc.*, **1990**, *112*, 8776., (b) Reich, H. J.; Borst, J. P. *J. Am. Chem. Soc.*, **1991**, *113*, 1835., (c) Bauer, W.; O'Doherty, G. A.; Schleyer, P. v. R.; Paquette, L. A. *J. Am. Chem. Soc.*, **1991**, *113*, 7093., (d) Bauer, W.; Sivik, M. R.; Friedrich, D.; Schleyer, P. v. R.; Paquette, L. A. *Organometallics*, **1992**, *11*, 4178.
9. This charge distribution was calculated by ESP (Electrostatic Potential) method.
   (a) Besler, B. H.; Merz, Jr, K. M.; Kollman, P. A. *J. Comp. Chem.*, **1990**, *11*, 431., (b) MOPAC 93 Manual.
10. Matsumoto, T.; Shioiri, T.; Ōsawa, E. *Tetrahedron*, the following paper.

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