ALLYLSILANES IN ORGANIC SYNTHESIS

HOMOALLYLIC ALCOHOL SYNTHESIS

and

ELECTROPHILIC ALKYLATION

by

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ABSTRACT

The chelating effect on regio- and stereochemical control of the homoallyl alcohol synthesis and electrophilic substitution of allylsilane was studied, using 2,2-dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (**S1**) and 2,2-Dimethyl-1-{1-[(S)-2-hydroxymethyl]pyrrolidinyl}-2-sila-4-pentene (**S2**), with **S1** synthesized from L-Prolinol.

The synthesis of homoallyl alcohol was carried out by allyl transformation from **S1** and **S2** to a Lewis acid activated aldehyde. Chelation between the allylsilyl ligand and the Lewis acid:aldehyde complex was found to favor the cyclic syn-clinal over the acyclic anti-periplanar transition state, in the asymmetric synthesis of the alcohol 1-dodecen-4-ol (**P1**). The bulky, remote and weak chelating ligand resulted in only modest selectivity and average chemical yield.

Regio- and stereochemical control of the electrophilic alkylation of allylsilanes **S1** were achieved due to chelating effect that favored α-alkylation. The chiral chelating ligand also resulted in enhanced stereochemical control electrophilic alkylation. Steric effect, due to a large electrophile, and solvent effect that causes disruption of the chelated complex, decrease α-selectivity.

RÉSUMÉ

On a étudié l'effet séquestrant sur le contrôle régio- et stéreo-chimique de la synthèse de l'alcool homoallyl et de la substitution électrophile de l'allylsilane en utilisant les composés diméthyl-2,2-{(methoxy-2-éthoxy)méthyl-2-(S)]pyrrolidinyl-1}-1-sila-2-pentène-4 (**S1**) et diméthyl-2,2-{[hydroxyméthyl-2-(S))]pyrrolidinyl-1}-1-sila-2-pentène-4 (**S2**), **S1** ayant été synthétisé à partir de L-prolinol.

La synthèse de l'acool homoallyl a été effectuée par transformation de l'allyl des composés S1 et S2 en un aldéhyde en présence d'un acide Lewis. Dans la synthèse asymétrique de l'alcool 1-dodecène-4-ol (**P1**), on a trouvé que l'effet séquestrant entre le ligand allylsilyl et le complex acide Lewis:aldéhyde est plus favorable à l'état de transition syn-clinal cyclique par rapport à l'état anti-périplane acyclique. Le ligand volumineux, éloigné, avec un faible pouvoir séquestrant a donné une sélectivité limitée et un rendement chimique moyen.

Le contrôle régio- et stéreo-chimique de l'akylation électrophile des allylsilanes **S1** a été obtenu grâce à l'effet séquestrant favorisant l'α-alkylation. Le ligand chiral séquestrant a aussi permis une amélioration de l'akylation électrophile avec contrôle stéréo-chimique. L'effet stérique à cause de l'électrophile volumineux, ainsi que l'effet de solvant qui détruit le complex séquestré réduisent la sélectivité pour la position α.

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Last but not least, I am always indebted to ALL my teachers, and professors whom, years after years have led me step by step steadily to new horizons of Knowledge. To these mentors I can never say enough, *thank you*.

To Mom, who, despite not seeing much of me, still keeps the food rations and saves a place for me.

PART 1

Chapter 1. HOMOALLYLIC ALCOHOLS SYNTHESIS

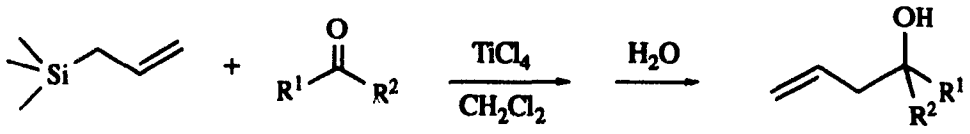
Silicon chemistry has recently been received increasing attention due to its versatility in organic synthesis [1]. The use of allylsilanes in the homoallylic alcohol synthesis and in electrophilic alkylation will be the objective of this project.

I. INTRODUCTION

Homoallylic alcohol is a versatile precursor in organic synthesis. It can be converted into other useful functional groups (eg., β-hydroxy acids [2]) or a starting substrate for natural product synthesis (eg., rifamycins [3]). Therefore, considerable interest has been generated in the field of homoallylic alcohols synthesis. Many routes to homoallylic alcohols [4-7] have been studied and research are focused on better control of the regio- and stereoselectivity, as well as the chemical yield, of the carbon-carbon bond formation step in these syntheses.

The use of allylsilane in the synthesis of allylic alcohols was first reported by Hosomi and Sakurai [8]. The reaction was carried out by using Lewis acid (LA) to catalyze the transfer of the allyl group on to a carbonyl compound (Scheme 1.1). Preliminary

Scheme 1.1 Homoallylic alcohol synthesis



studies by Hosomi and Sakurai, and later on by other groups [15, 21], have proven the regiospecificity of the allylation of carbonyl compounds. It has been found to occur

exclusively at the γ-carbon of the allyl moiety, which has high reactivity towards electrophiles due to the hyperconjugative overlap of the σ*(Si-C) bond with the (C-C)π system. As this (hyperconjugation) occurs, it raises the HOMO energy of the molecule and makes allylsilanes more reactive towards electrophiles [9].

Continuing research has been since carried out to improve the yield and stereoselectivity of the reaction. Parameters that are apt to variation such as the Lewis acids, allylic silanes, aldehydes, reactions conditions, etc., have been accordingly studied. Steric factors, as well as chiral auxiliaries, have also been introduced, on the participating reagents, in order to induce asymmetric synthesis. Mechanistic details, however, are still somewhat ambiguous since the outcomes are depending on the intrinsic properties of the reagents in these reactions.

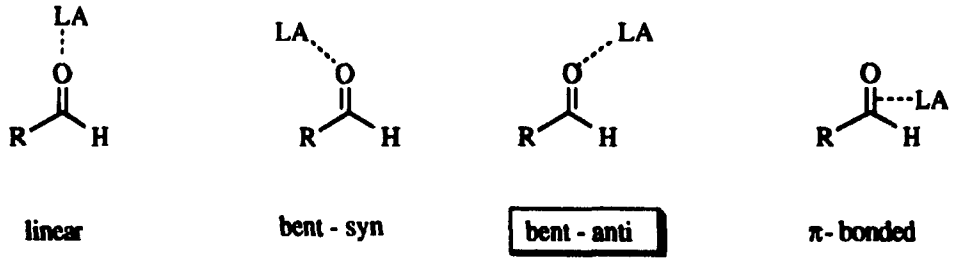
II. LEWIS ACID CATALYSIS [10]

Primarily, a Lewis acid was used to activate the carbonyl center as it is coordinating with the carbonyl oxygen. A Lewis acid, by definition, is an electron acceptor from a Lewis base which is a donor. The donor in this case is the carbonyl oxygen of the aldehyde. It has been proposed that functional groups are more susceptible to nucleophilic attack due to an enhancement of electrophilicity through complexation with a Lewis acid. Thus, upon coordinating with the Lewis acid, the aldehyde becomes a ligand of the metal in the Lewis acid complex. The metal - ligand bond affects the polarization of the C=O bond as the metal accepts electron density from oxygen. This coordination, therefore enhances the polarization of the C=O bond, increases C=O bond length and the electrophilicity at the carbonyl carbon. Nucleophilic attack, by nucleophile such as allyl, at that activated carbon center is therefore enhanced. The Lewis acid can also stabilize the leaving group, and contribute favorable entropy effect (by "tying" - coordinating - reactants together) which

result in an activated reactive system [10a]. As the coordination bond is generally thermally labile, these syntheses are usually carried out at low temperature [4-8, 10].

Recently there have been efforts in studying the geometry of the Lewis acid-oxygen (of the C=O group) coordination bond [10b-e]. There are four possible modes of bonding as shown in scheme 1.2. Experimental results [10c,e] and *ab initio* calculations [10b,d] have shown the most stable mode of coordination between the LA and the oxygen of the aldehyde to be of the bent configuration with the metal atom of the LA lying on the nodal plane of the C=O π-bond. Moreover, for aldehydes, a complex with the LA anti to the R group also is more favored than the syn configuration, satisfying both steric and electronic demand [10b-e].

Scheme 1.2 Modes of coordination of Lewis acids to aldehydes



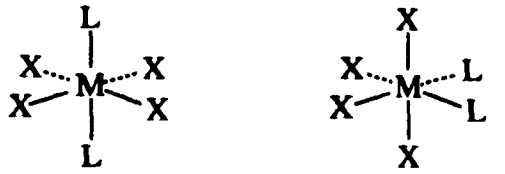
III LEWIS ACID - LIGAND COORDINATION AND STRUCTURE

Titanium tetrachloride ($TiCl_4$), and marginally less so, stannic tetrachloride ($SnCl_4$) are among the relatively strong Lewis acids commonly used in organic synthesis. At oxidation number of +4, both can have a maximum coordination number of 6. This means that in a reaction medium, the Lewis acid can bond with two more ligands affording an

octahedral adduct, complex $MX_4.2L$ (M : metal center, X : halogen ligand, L : carbonyl ligand).

Extensive spectroscopic studies by Zahrobsky [11], Beattie [12] and Merbach [13] have provided informations on the structure and stability of these complexes. It is found that, based on electronic effect [13], the cis-isomer are almost exclusively favored for ligand types including carbonyl and linear ether. These ligands are considered weaker than the halides in competing for the metal empty d_π-orbitals. Therefore, to maximize the p_π-d_π overlap between its filled p-orbitals and the metal empty d ones, the halogens will rearrange themselves, avoiding facing each other to compete with a weaker ligand. Thus a cis geometry is favored. Conversely, when L is a better donor, and better competing for the metal d-orbital, such as hexamethylphosphoramide (HMPA), a trans configuration is favored over the cis .

Scheme 1.3 Geometry of $MX_4.2L$ complexes.



$MX_4.2L$ - *trans* $MX_4.2L$ - *cis*

Sterically [11,12], a less bulky ligand will also favor cis configuration as the four halogen ligands, in a pseudo-tetrahedral space, rearrange to have minimized steric interaction with each other. A more bulky ligand will result in a trans configuration for the same effect.

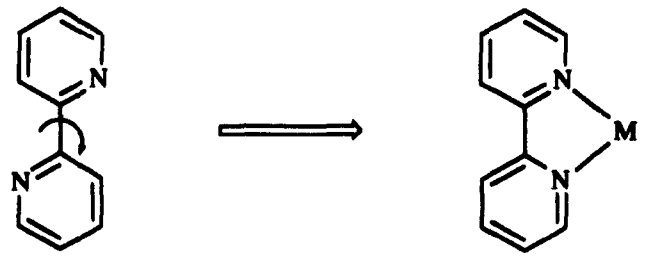
Tin, with a full electron-occupying d shell, has weaker p_π-d_π interaction with ligands than Ti which has only two d-electrons in the shell. Thus for $SnCl_4.2L$, steric effect will most probably dominate over electronic effect in determining the adduct configuration, and has lower barrier to cis-trans isomerization.[13]

IV. CHELATING EFFECT [14]

Using ligands with more than one coordinating site will result in a chelate complex with the Lewis acid. Chelated complexes are found to be kinetically and thermodynamically more stable with respect to ligand displacement, compare to non-chelated ones [14a] . In a chelated complex, a bidentate Lewis base (eg. aldehyde) will obviously have the cis-configuration (Fig. 1.1). The formation of a chelated complex is

Figure 1.1 Chelated complex of Lewis acid and bidentate ligand

sequential formation of M-X and M-Y bond



2,2'-bipyridine

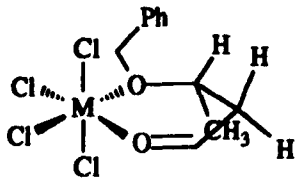
transoid
(most stable conformation)

cisoid
(in chelated complex)

found to follow an Eigen-Wilkins pathway in which the metal-ligand bond is formed sequentially [14d] . Thus, a ligand may have to adopt a conformation that is not the most stable one in its isolated state. For example , 2,2'-bipyridine is cisoid when it is chelated to a metal atom of a Lewis acid, contrary to its normal transoid conformation. Thus, formation of a chelated complex also result in the formation of heterocyclic rings, in which one of the heteroatoms is a metal. These heterocycles, which normally have favored conformations, therefore introduce new conformational possibilities for the the ligands [14d]. Since rotation about the O-M bond is generally facile [10b,d] chelated complexes therefore offer more rigidity, or the ligands can be said to be "conformationally lock" [15a] . If the multidentate ligand is also chiral, an enhanced facial selectivity can also be achieved with the chelated complex [16] .

The hexacoordinated Lewis acids are found to be good acceptors for multidentate and chiral ligands in forcing the reactive centers to be closer together (compare to the 4-coordination LA, for example, where it is less crowded) [10b] . Of these, $TiCl_4$ and $SnCl_4$ are the relatively stronger and frequently used Lewis acids. It was found that, for the system shown in figure 1.2, the chelated complex formation is favored at low temperature for both $TiCl_4$ (from -20 to -80°C) and $SnCl_4$ (<-93°C) [15a] . The relatively lower temperature required to observed a complex formation for $SnCl_4$ can be accounted for due to the Lewis acid's softness (fully occupied d-shell of Sn) compare to $TiCl_4$ which can form stronger metal-ligand bond [15].

Figure 1.2 Chelate complex of $TiCl_4$ and $SnCl_4$

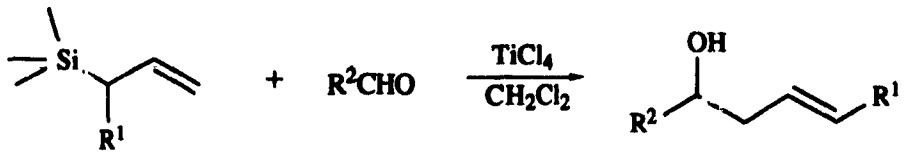


M= Ti, Sn

V. LITERATURE REVIEWS

Although reports by Hosomi and Sakurai [8] were not conclusive about the cyclic transition state (TS) of the allylic transformation, they, however, unambiguously proved that the C-C bond formation occurred regiospecifically at the γ-carbon of the allyl.(Scheme 1.4). Stereoselectivity of the reaction was not elaborated.

Scheme 1.4 Regioselectivity of homoallyl acohol synthesis [8].



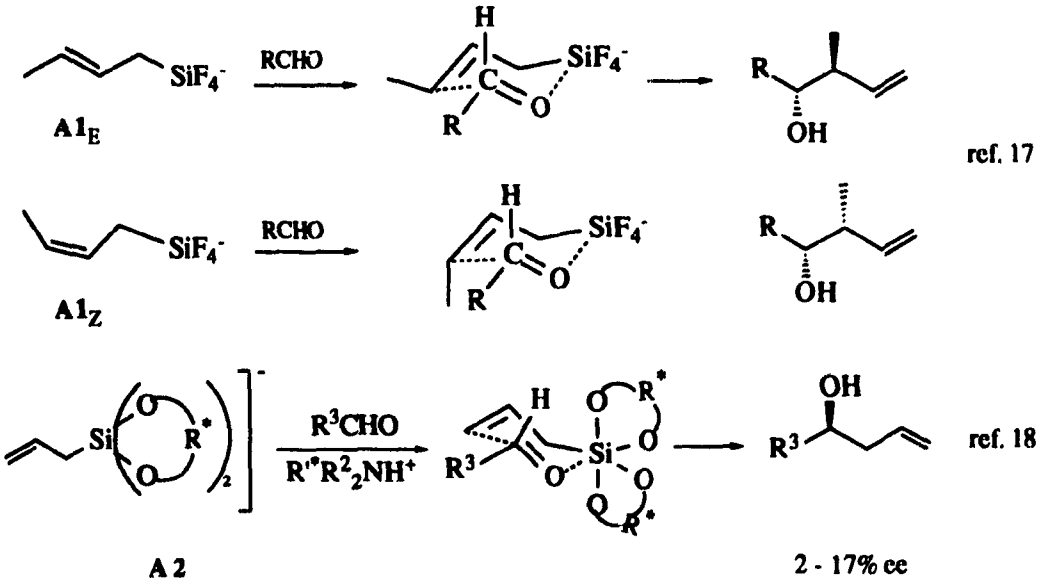
R^1 = Me, Ph R^2 = n-C_4H_9 only product

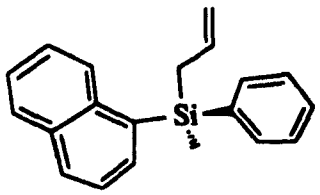
Perhaps the only instance where a Lewis acid was not needed is when pentacoordinated allylsiliconate was used. The stable pentacoordinate allylsiliconates **A1** [17] and **A2** [18] have significant Lewis acidity and the nucleophilicity of the allylic γ-carbon is enhanced compared with the usual tetracoordinated silicon. Thus, it reacts with an aldehyde via a six-membered cyclic transition state (Scheme 1.5) with the silicon acting as

both a Lewis acid center and allyl bearing atom. Stereoselectivity is modest in these reactions.

Si-centered chiral allylic substrate **A3** was used by Hathaway and Paquette [19]. It was found that **A3** was more susceptible to destruction by certain Lewis acid catalysts ($TiCl_4$ and $SnCl_4$ included) than to react with a carbonyl center. Moreover, the aryl groups substituent about the silicon center appeared to have great steric encumbrances and adverse electronic contributions to the allylic transformation reactior. These factors diminished the reactivity of **A3** and resulted in low ee (0-5%) and chemical yield (0-20%). This finding has deterred others on using Si-centered chiral substrate for the asymmetric synthesis of homoallylic alcohols.

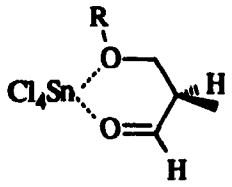
Scheme 1.5 Homoallyl alcohols from pentacoordinate allylsiliconates





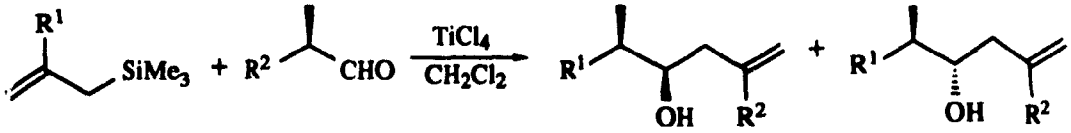
A 3

Heathcock et al. [20], using chiral aldehydes, were able to induce diastereoselectivity in the allylic transformation to aldehydes of up to 38% diastereomeric excess (de). Their results (Scheme 1.6) are consistent with the Felkin model [21] for nucleophilic attack at a carbonyl carbon α to a chiral center. This model also proposed an acyclic transition state (Scheme 1.7). An improvement in diastereoselectivity (75% de) was achieved with additional steric constraint on the allyl moiety (ii), and using chelating aldehyde **A4**.



A 4

Scheme 1.6 Homoallyl alcohols from chiral aldehydes [20].

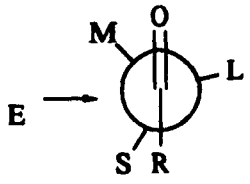


i : R^1= H a : R^2= Ph

ii : R^1= Me b : R^2= $PhCH_2OCH_2$

Allylsilane	Aldehyde	Lewis acid	Yield (%)	dc (%)
i	a	$TiCl_4$	86	23
		$BF_3.OEt_2$	47	33
		$SnCl_4$	86	38
ii		$TiCl_4$	66	47
		$BF_3.OEt_2$	64	75
		$SnCl_4$	68	52
i	b		92	85
		$BF_3.OEt_2$	0	
ii	b	$SnCl_4$	83	82

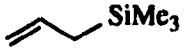
Scheme 1.7 Felkin's model for nucleophilic attack at an aldehyde α to a chiral center [21].



M = medium = Me

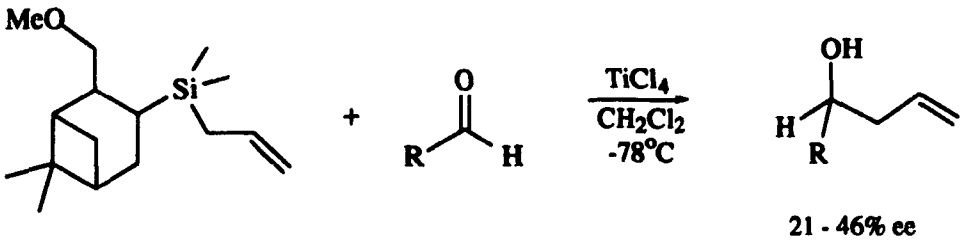
L = Large = Ph

S = small = H

E = 

C-centered optically active allylsilane such as **A5** in which a chiral center is α to Si and on a non allylic ligand was employed by Coppi et al.[22] and asymmetric induction of up to 46% enantiomeric excess (ee) was observed with various aldehydes, using $TiCl_4$ as the catalyst (Scheme 1.8).

Scheme 1.8 Homoallyl alcohols from C-centered chiral silicon substituent allylsilane [22].



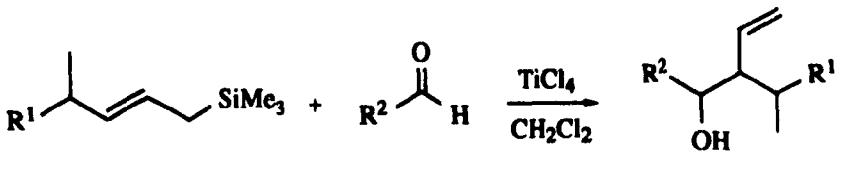
A5

21 - 46% ee

39 - 61% yield

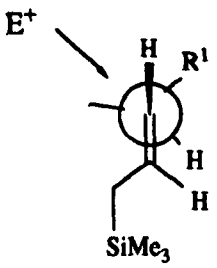
Allylsilane having a chiral center α to the double bond and the Si center was the substrate of study by Taddei [23] (Scheme 1.9). The stereoselection results were rationalized based on a model by Houk [24] (Scheme 1.10) for the electrophilic attack to a double bond adjacent to a chiral center. An acyclic transition state was suggested by this model. When electronic effect is not important, steric hindrance will dictate the stereoselective outcome of the attack. Using allylsilane with a chiral center α to both allyl and silicon, Kumada [25] also suggested an acyclic transition state (Scheme 1.11). This proposed transition state was based on an S_E' mechanism for allylsilane [25] in which the silyl moiety, also a leaving group, is anti to the incoming electrophile. However, an acyclic syn-clinal transition state was suggested [26] that could also account for the same results (Scheme 1.11).

Scheme 1.9 Homoallyl acohols from allylsilanes with chiral center α to allyl and remote from Si [23].

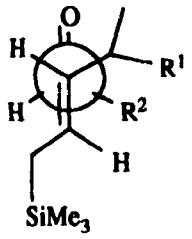


A 6

ee varies

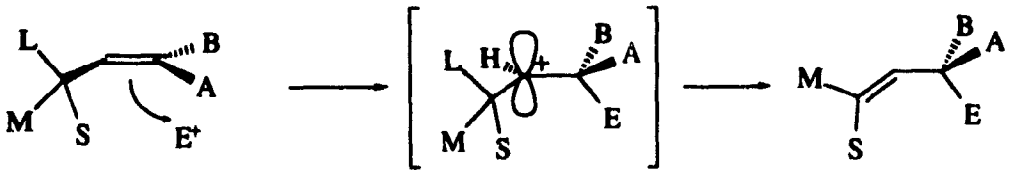


Houk's model for electrophilic attack



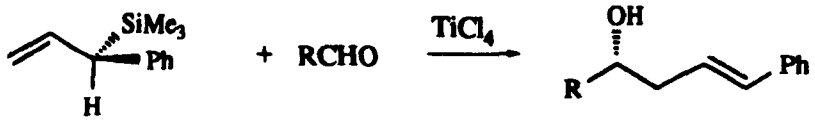
Anti-periplanar transition state after Houk's model

Scheme 1.10 Houk's model for electrophilic attack to a double bond adjacent to a chiral center [24].



If L = leaving group = largest group then an E-alkene will result from the anti stereoselectivc addition.

Scheme 1.11 Homoallyl alcohols from allylsilane with a chiral center a to both allyl and Si [25]



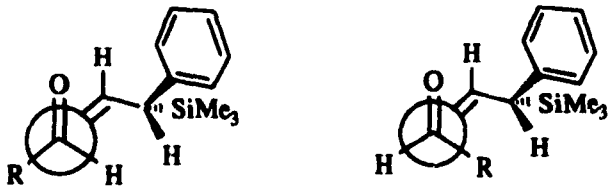
A 7

Anti-periplanar transition state

sterically favored

ee of allyl silane (%)	R	Yield (%)	ee (%)	Abs. conf.
95	t-Bu	71	91	R
90	t-Bu	67	73	R
95	i-Pr	66	91	R
85	i-Pr	63	84	R
91	Me	83	64	S

Syn-clinal transition state

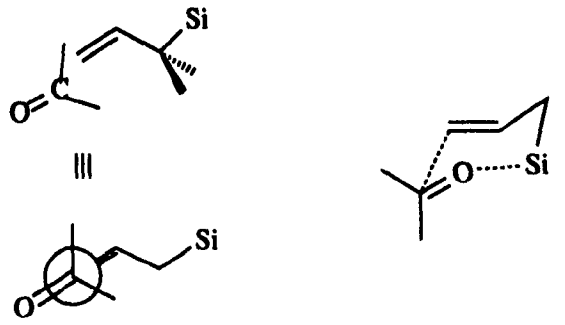


sterically favored

to give the same results as anti-TS

Detailed studies by Denmark [27] took into consideration the important stereocontrol effect of Lewis acid-aldehyde complexation. It was found that a cyclic syn-clinal transition state was also possible.(Scheme 1.12). With $SnCl_4$ as the Lewis acid for the allylation of

Scheme 1.12 Transition state models for homoallylic alcohols synthesis

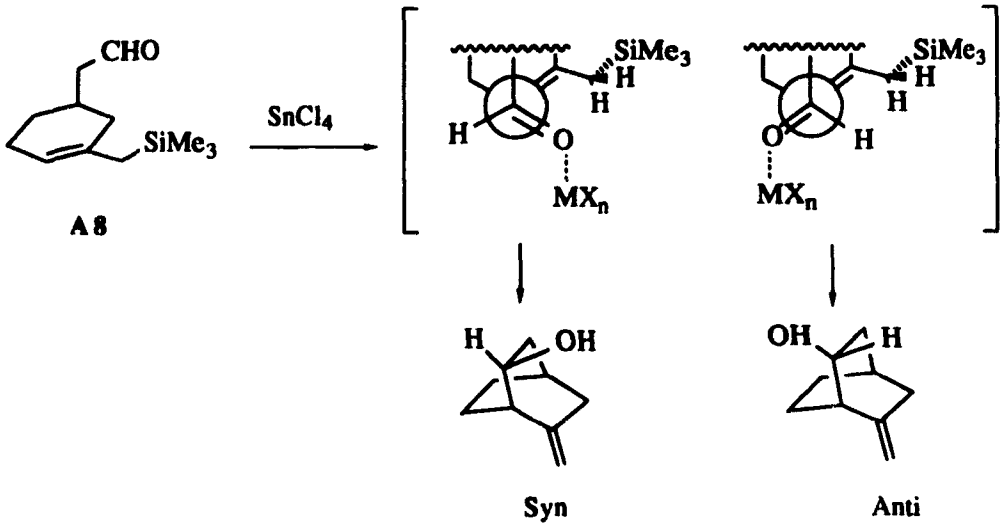


acyclic
anti-periplanar

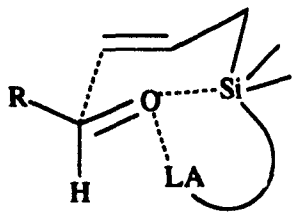
cyclic
syn-clinal

A8, a syn product was favored at dilute solution, at high Lewis acid to aldehyde ratio and with a less steric hindered Lewis acid-aldehyde complex (Scheme 1.13).

Scheme 1.13 Effect of LA:RCHO coordination on transition state [27]



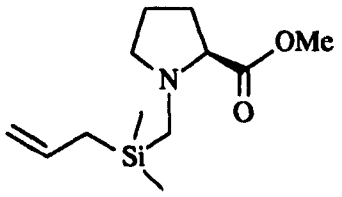
Base on these results, in order to favor the syn-clinal transition state, Wang and Chan [28] used allylsilane reagents that had a chiral coordinating ligand remote from the silicon center. These substrate were expected to coordinate with the Lewis acid and induce



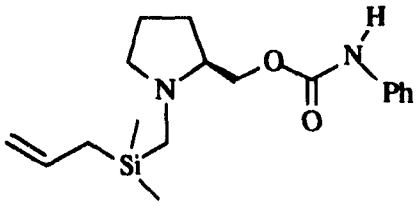
A9

stereoselectivity in a syn fashion as shown by **A9**. Therefore, using allylsilanes **A10, A11, A12, A13** as in Scheme 1 with nonyl aldehyde, they were able to study the chelating effect on the asymmetric synthesis of the homoallylalcohol synthesis. This type of

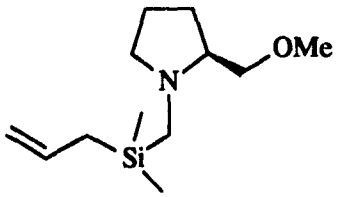
allylsilane substrate also did not have significant steric interference as with **A3, A5, A6, A7**. Thus it was found that when a large amount of chelating Lewis acids (such as $TiCl_4$ and $SnCl_4$) was used, chelation was disrupted and chelated complex (such as **A9**) became less populous, which resulted in lower ee (entries 3 and 4, table 1.1). On the other hand, the ee was unchanged when excess amount of $BF_3.Et_2O$ was used (entries 6 and 7, table 1.1) since this is a poor chelating LA and [16b], therefore, insensitive to chelating effect.



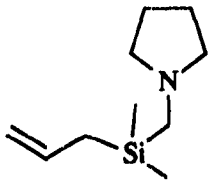
A10



A11



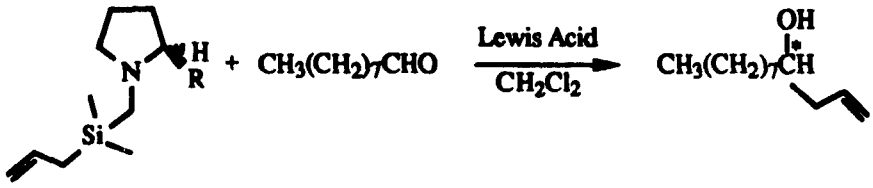
A12



A13

Thus with highly chelating.Lewis acid or Lewis base system such as $TiCl_4$ and **A11**, the ee was better than non-chelating one, such as $BF_3.Et_2O$ or **A13** (Table 1.1). The results from this study appeared to favor a cyclic synclinal transition state.

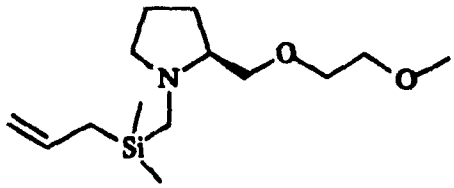
Table 1.1 Chelation effect on ee in the synthesis of 1-dodecen-4-ol [28]



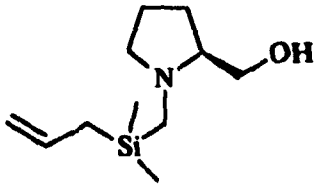
Entry	R	Lewis acids	Equiv.	T (°C)	Time (hrs)	Yield (%)	ee (%) [a]	Abs. conf.
1	$-CO_2CH_3$ (A10)	$TiCl_4$	1	-50	20	<5		
2			2	"	"	60	43	S
3			3	-50	"	61	43	"
4			10	"	3.5	79	28	"
5			3	-70	30	63	36	"
6		$BF_3.Et_2O$	4	-50	24	58	30	"
7			10	"	3	51	30	"
8		$SnCl_4$	"	"	"	73	41	"
9	$-CH_2OCONHPh$ (A11)	$TiCl_4$	"	"	25	57	45	"
10		$SnCl_4$	"	"	40	<5		"
11	$-CH_2OCH_3$ (A12)	$TiCl_4$	"	"	18	70	37	"
12	H (A13)	"	"	"	20	<5		"

a) Determined by optical rotation

Following the same line of approach, allylsilanes 2,2-dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (S1) and 2,2-Dimethyl-1-{1-[(S)-2-hydroxymethyl]pyrrolidinyl}-2-sila-4-pentene (S2) have been used to study further the advantage of chelating effect from the allylsilane moiety in the synthesis of homoallylic alcohols. The results of this study are presented and discussed following the next chapter.



S1



S2

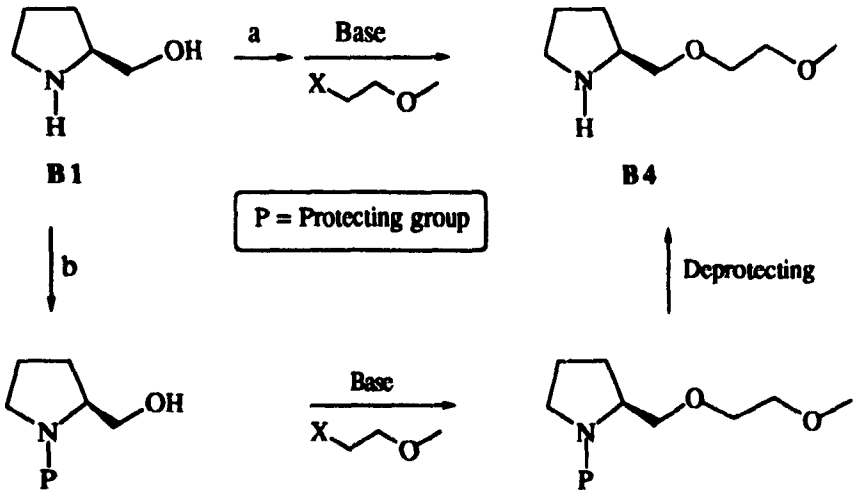
Chapter 2. SYNTHESIS OF THE STARTING MATERIAL

2,2-Dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (S1)

I. THE *sec*-AMINE: TO PROTECT OR NOT TO PROTECT

A scheme was devised for the synthesis of the starting reagent S1 (Scheme 2.1) from the commercially available L-prolinol or (S)-(+)-2-pyrrolidinemethanol (C1). At first, the short-cut route (a) was tried with the hope that the protecting step of the secondary amine could be bypassed. That would be achieved if the competing reactions between O- and N-alkylation could be controlled by lowering the reaction temperature. Therefore, it

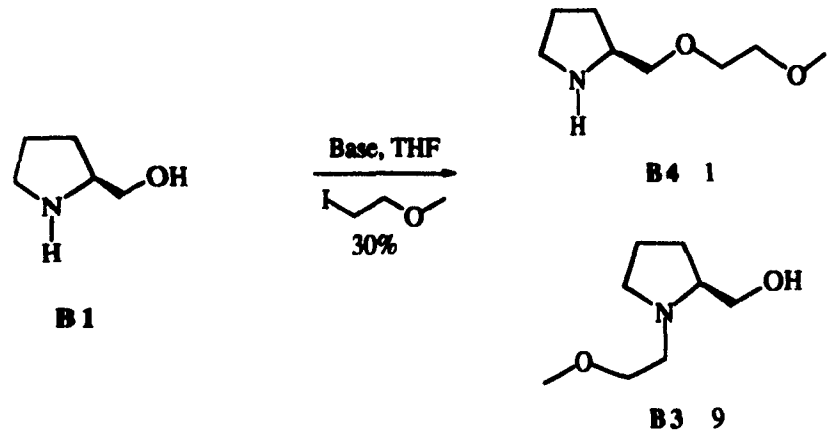
Scheme 2.1 Synthesis scheme for B4



was expected that the oxy-anion of prolinol, generated in situ by a hydridic base, would be more reactive than the *sec*-amine toward an electrophile. As it turned out, the reactivity of both the oxy-anion and the secondary amine was very low toward the electrophile 2-iodoethyl methyl ether (B2). As the temperature was raised up to refluxing alkylation occurred in favour of N-alkylated product (S)-1-(2-Methoxyethyl)-2-hydroxymethylpyrrolidine (B3) (Fig. 2.1a, b) with the molar ratio of N- to O-alkylation, which gave S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (B4) (Fig. 2.2a, b), of 28:3 for a

combined yield of 30% [29] (Scheme 2.2). Therefore, protecting of the secondary amine was necessary.

Scheme 2.2 O-Alkylation of L-Prolinol



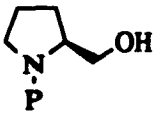
B1

B4 1

B3 9

II. CHOOSING N-PROTECTING GROUP

An N-protecting group must be chosen so that it can withstand the basic condition of the alkylating step. It must react with the amine selectively and be removed easily. A few N-protecting groups were considered and the results are shown in table 2.1.

Table 2.1 N-Protected Prolinol 

Entry	N-Protecting group P	Yield (%)	Compound
1	$PhCH_2$-	46	B5
2	$PhCH_2OCO$-	85	B6
3	-SO_2-	30	B10
4	-CHO	97	B12

Figure 2.1a ^{1}H NMR Spectrum of (S)-1-(2-Methoxyethyl)-2-hydroxymethylpyrrolidine (B3).

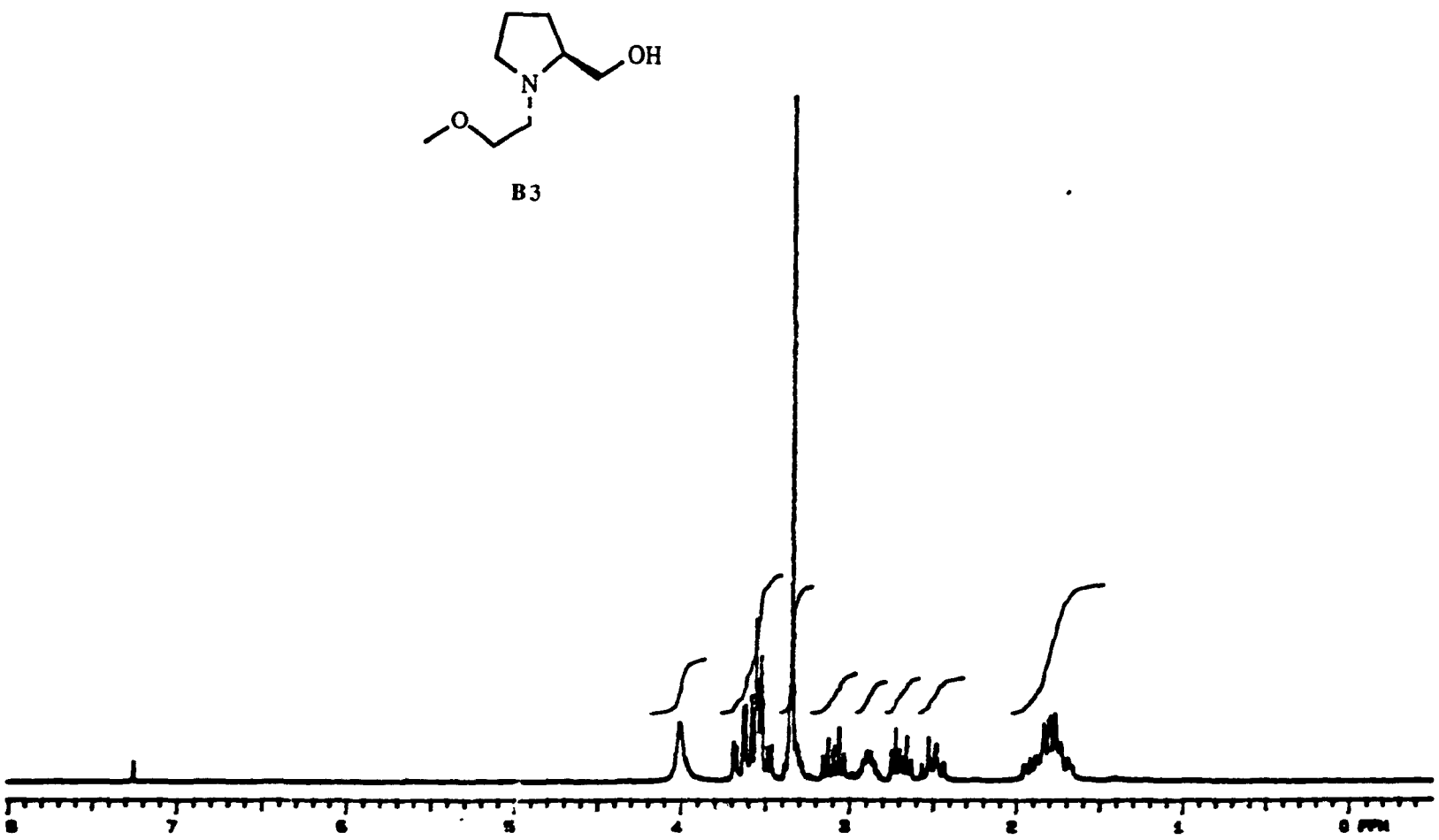


Figure 2.1b ^{13}C NMR Spectrum of (S)-1-(2-Methoxyethyl)-2-hydroxymethylpyrrolidine (B3).

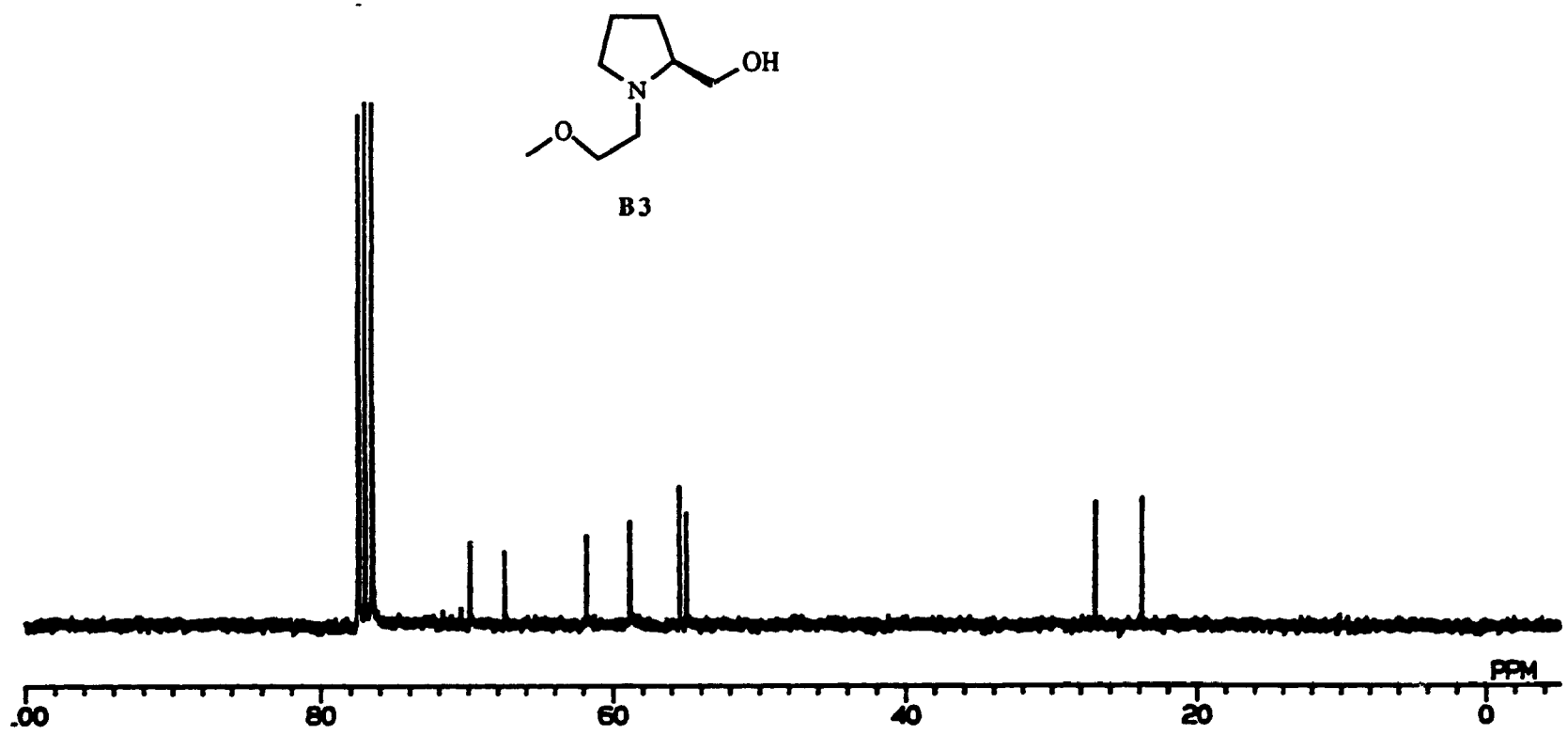
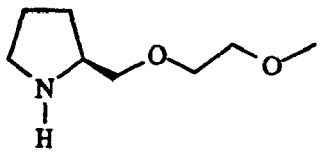


Figure 2.2a ^{1}H NMR Spectrum of S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (B4)



B4

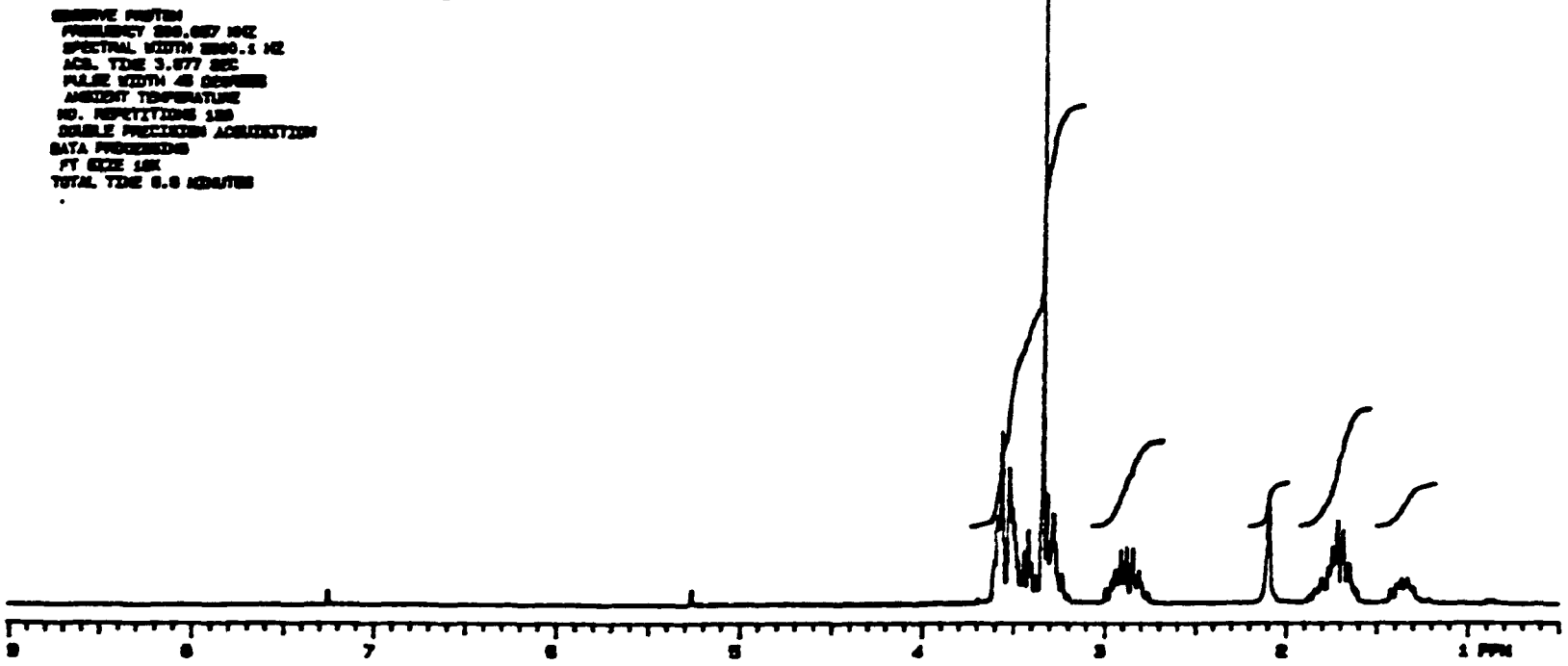
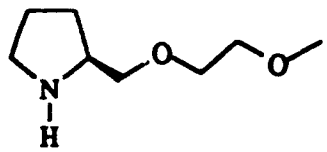
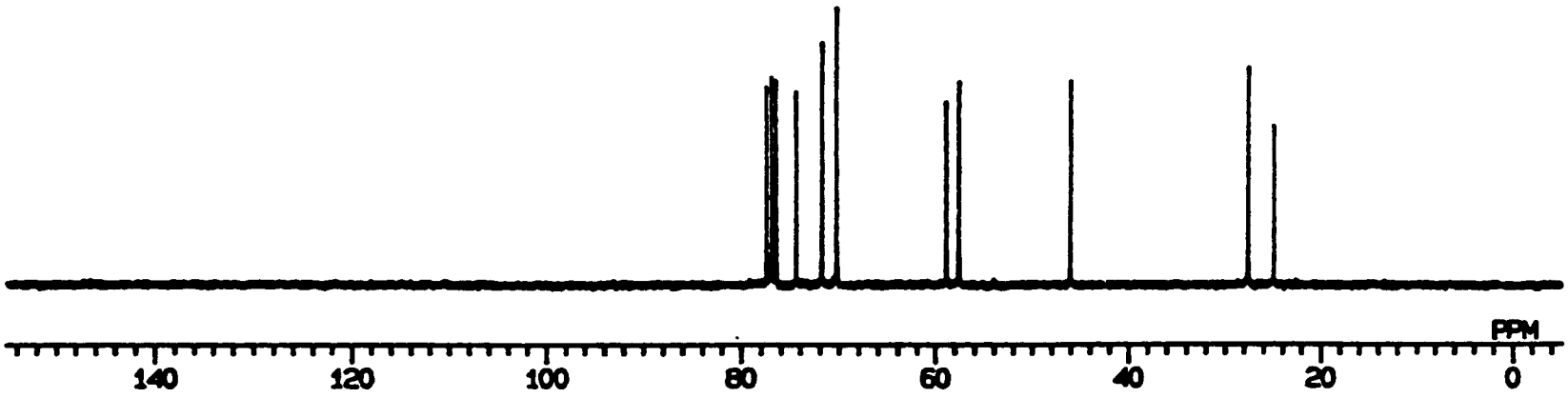


Figure 2.2b ^{13}C NMR Spectrum of S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (B4)



B4

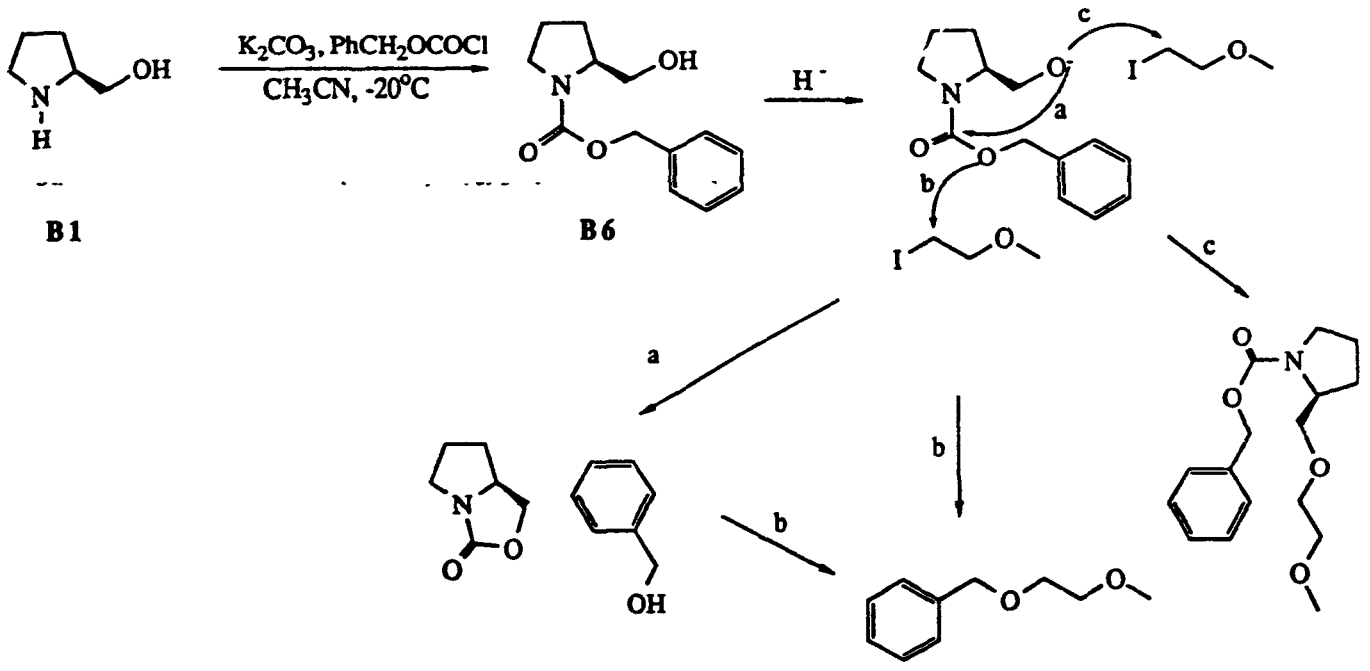


The protecting step of the nitrogen, considered the first in a multisteps synthesis of the starting reagent, must therefore be of reasonably high chemical yield. With only 46% yield the benzyl group [30] (entry 1 in table 2.1) was excluded as a protecting group of choice for the amine in study.

The carbobenzoxy (CBZ, $PhCH_2OCO$-) group is a well known N-protecting group [31] and had a relatively high yield in the synthesis of (S)-1-carbobenzoxy-2-hydroxymethylpyrrolidine [32] (**B6**). However, the CBZ group was undesirable since it was sensitive to the basic condition of the O-alkylation reaction. The CBZ group was cleaved and formed side products **B9**, benzyl alcohol and **B8** predominantly over the desired product **B7**, with a molar ratio of (10:59:27:4) respectively, for a combined 56% chemical yield (Scheme 2.3).

Sulfuryl chloride (SO_2Cl_2), on the other hand, is probably better known as a chlorinating agent [33] for carbonyl, sulfoxide and alkene, than as an N-protecting group. As used in this case, SO_2Cl_2 presented an interesting approach : the alkylation step of **B10** could be carried out under acidic condition in a nucleophilic substitution reaction [34, 35]. Removal of the sulfamide protecting group then could be carried out under basic condition (Scheme 2.4) to give **B4**.

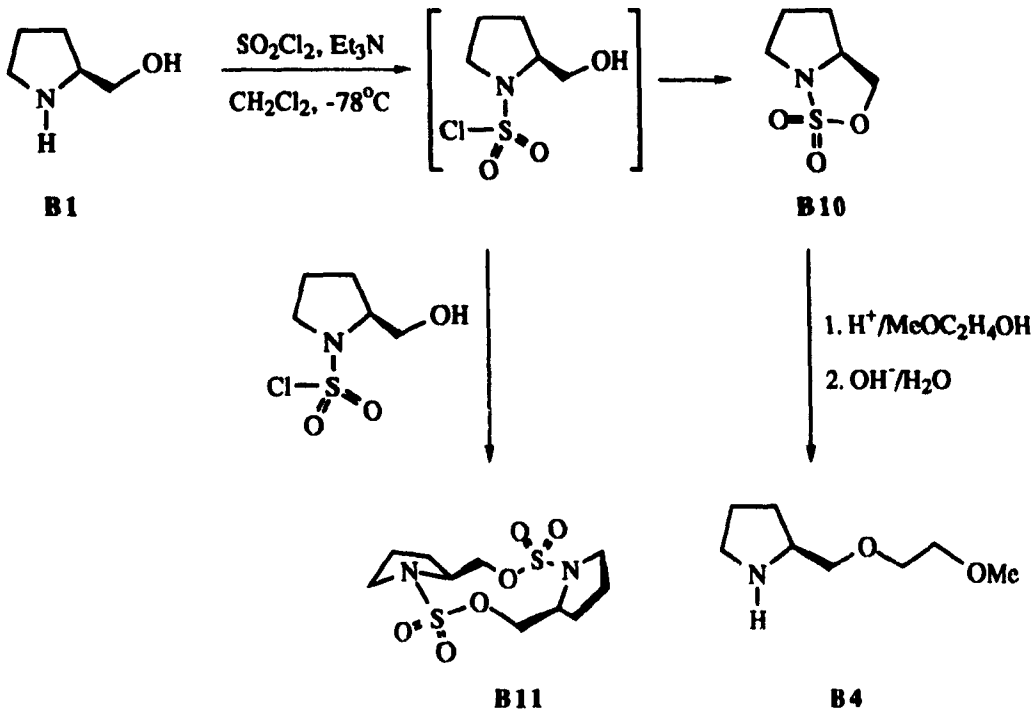
Scheme 2.3 O-Alkylation of (S)-1-Carbobenzoxy-2-hydroxymethylpyrrolidine (B6)



B1 **B6**

	B9	Benzyl alcohol	B8	B7
56% :	10	59	27	4

Scheme 2.4 Sulfuryl Chloride (SO_2Cl_2) as N-protecting group



B1 **B10** **B11** **B4**

The disadvantage of this approach was that the synthesis of **B10** is a cyclization reaction. Therefore, high volume of solvent must be used to ensure the necessary dilution for only intramolecular reaction to occur. This is certainly not practical for large scale synthesis. Under the conditions that were used, the dimerised product **B11** was isolated in a molar ratio of 1:9 to the desired product **B10** for a combined yield of 30%.

The formyl group (-CHO) was then left as the best N-protecting group for L-prolinol, and **B12** could be obtained from a neat reaction between L-prolinol and ethylformate (1.1 eq.) in 97% yield. Under mild basic condition [36], the formyl group can be removed in quantitative yield.

III. ELECTROPHILIC O-ALKYLATION

This is the most important step in the synthesis of **S1**. As mentioned earlier, although this is an S_N2 reaction of a primary alcohol and a primary electrophile, a rather "vigorous" condition, i.e., refluxing, was needed for the reaction to occur. Two electrophiles were considered: iodoethyl methyl ether (**B2**) [37] and 2-methoxyethyl tosylate (**B13**). The results shown in table 2.1 demonstrated that difficulty. Even with tosylate, considered one of the best leaving group, the maximum yield for **B14** (Fig. 2.3) was only 78% [38], although an improvement of 20% from using **B2** as the electrophile was encouraging [39].

Removal of the formyl group was carried out under mild basic condition give **B4** in relatively high yield.

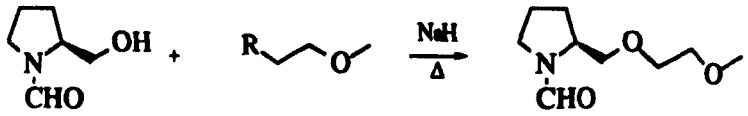
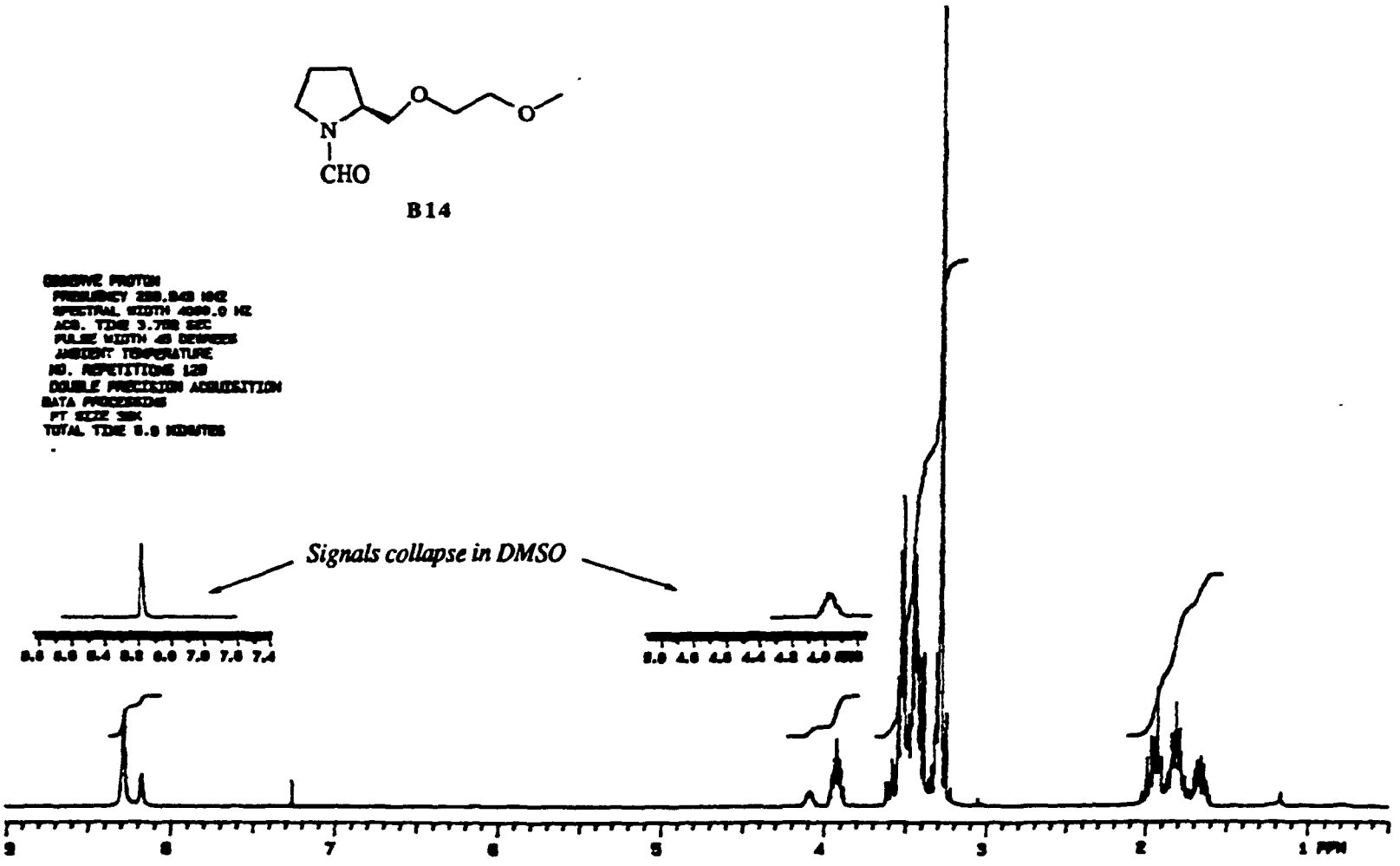


Table 2.2. O-Alkylation of N-Formyl--S-2-hydroxymethylpyrrolidine (B12)

R	Solvent	Yield (%)
I	THF	56
I	DMF	<50 (crude)
TsO	THF/DMF	78

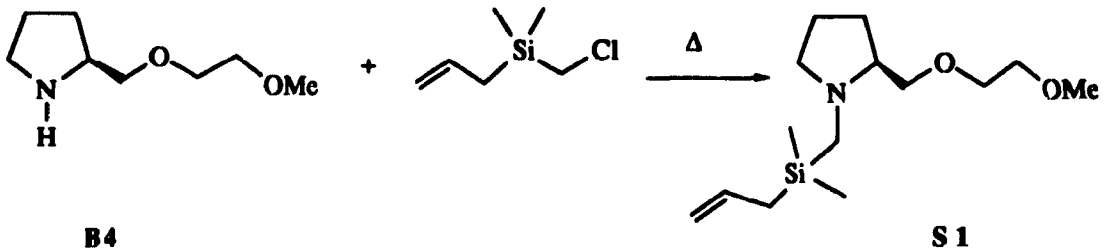
Figure 2.3 ^{1}H NMR Spectrum of (S)-1-Formyl-2-[(2-methoxyethoxy)methyl]pyrrolidine (B14)



IV. THE FINAL STEP

The last step of the synthesis of the starting reagent **S1** was carried out by a simple reaction of the neat mixture between **B4** (2eq.) and the commercially available allylchloromethyldimethylsilane (1eq.) (Scheme 2.5)

Scheme 2.5 Synthesis of S1



B4 **S1**

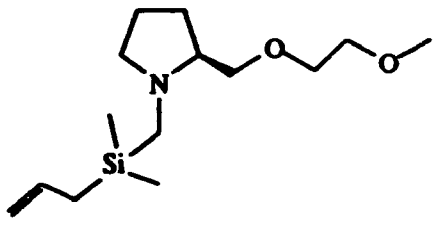
Conditions	Yield (%)
110°C, o/n	34
NaI, 110oC, o/n	59
NaI, 3Å sieves, 90-110°C, 2hrs	90

Under normal reaction conditions (heating overnight at 110°C), the yield of **S1** was modest (34%). To improve the yield of the reaction, catalytic amount of sodium iodide was added to activate the poorer leaving group chloride. An improvement of 25% in chemical yield was achieved, leaving it at 59%, which was far from quantitative. It's known that proline is one of the few natural amino acids that are very readily soluble in water. Proline derivatives, such as prolinol and unfortunately, **B4**, are also hygroscopic. Therefore it was probable that a high percentage of **B4** could be present in the reactive

medium as RNH^+OH^-, thus lowering the reaction yield. Distillation of **B4** under anhydrous condition could solve the problem. However, using molecular sieves in order to remove water in situ was preferred since it avoids the need for distillation. Thus, with the "double effect", using cat. NaI and molecular sieves, the reaction had been improved from 39% to an acceptable 90% chemical yield. S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (**B4**) was recoverable from its hydrochloride salt by basic extraction with aq. NaOH 10%.

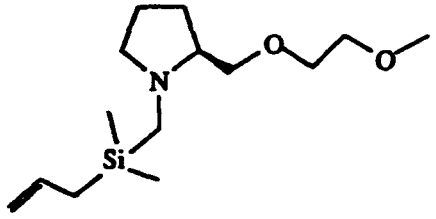
The synthesized starting reagent **S1** (Fig. 2.4a, b, c) henceforth must be kept in an inert medium, such as benzene and flushed with argon, and stored at low temperature to prevent the formation of the tertiary N-oxide product. The source of oxidant can easily be ambient atmosphere!

Figure 2.4a ^{1}H NMR Spectrum of 2,2-Dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl] pyrrolidinyl}-2-sila-4-pentene (S1)



S1

Figure 2.4b ^{13}C NMR Spectrum of 2,2-Dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl] pyrrolidinyl}-2-sila-4-pentene (S1)



S 1

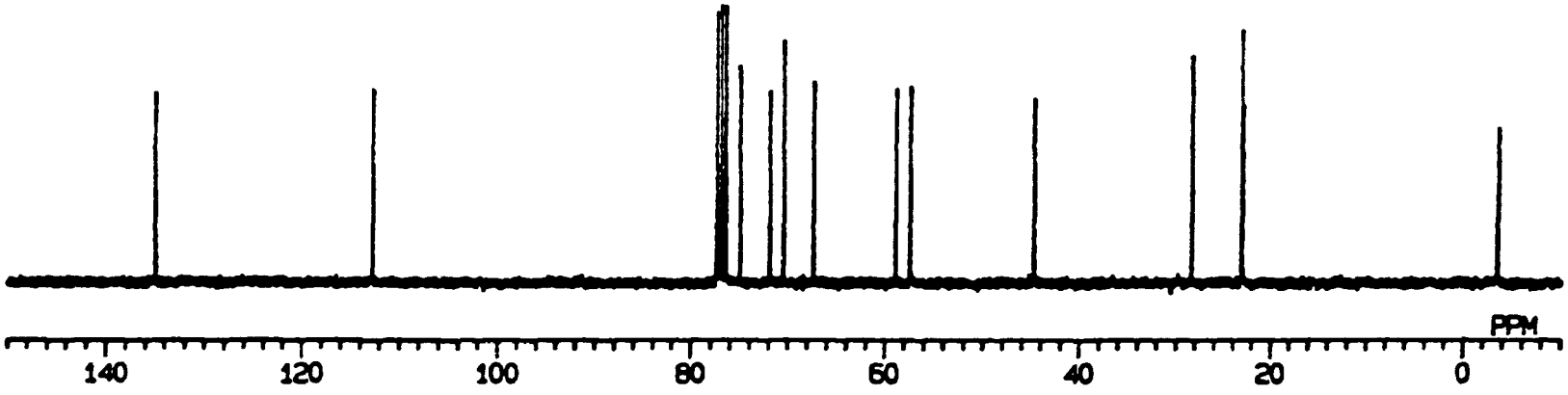
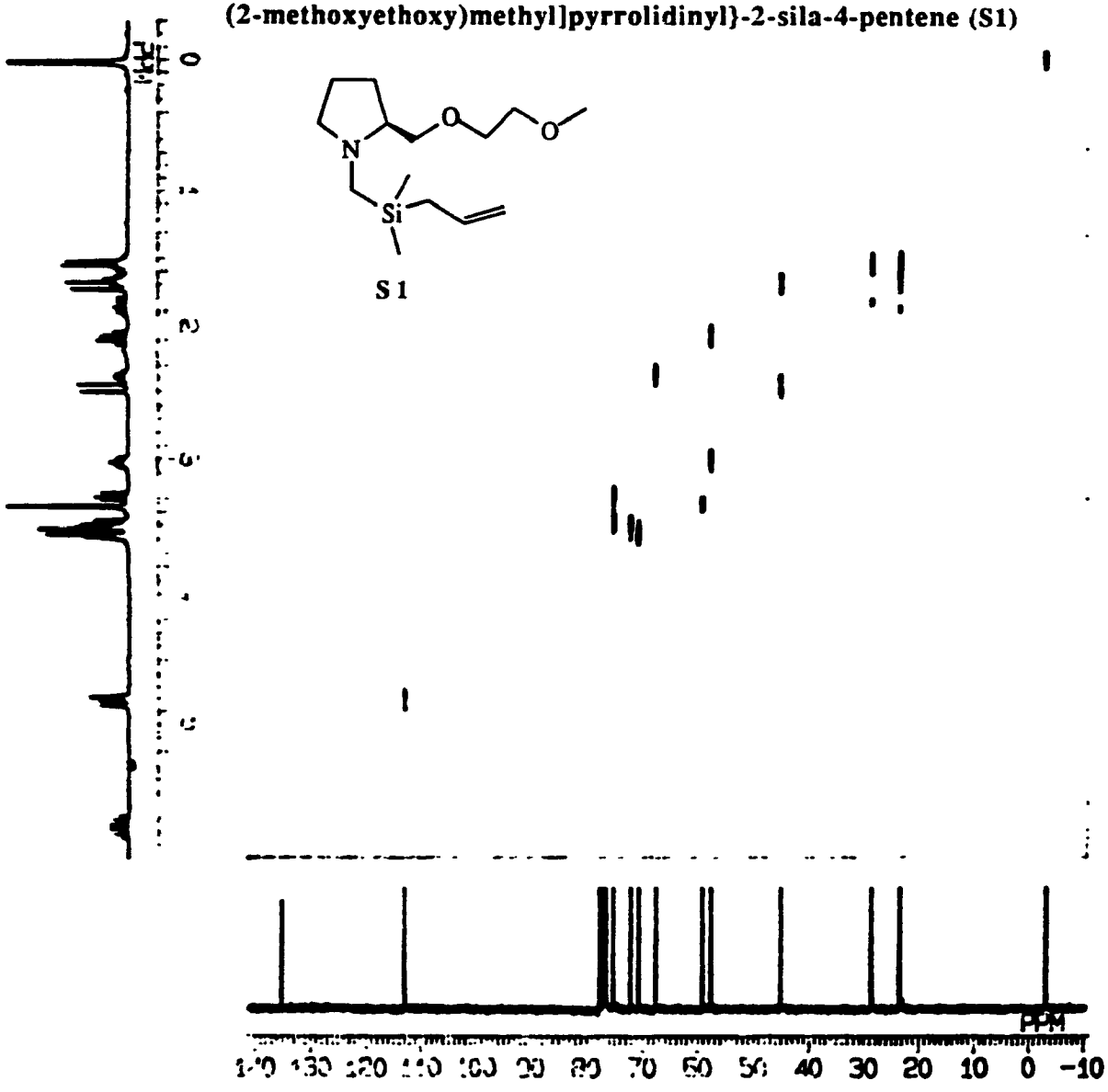


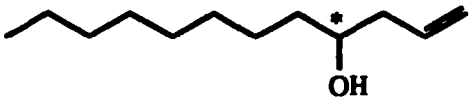
Figure 2.4c HETCOR Spectrum of 2,2-Dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (S1)



Chapter 3. RESULTS and DISCUSSIONS

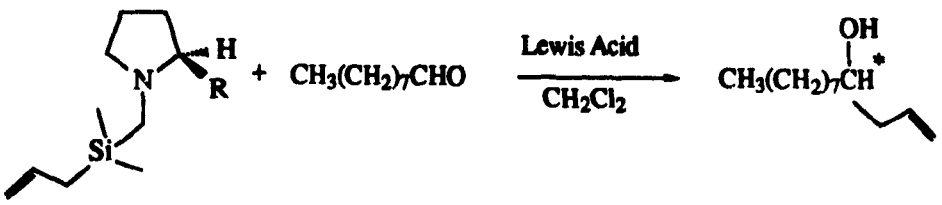
Homoallyl Alcohols Synthesis

Results from Denmark [27] and Chan [28] led to the decision to use the two better coordinating Lewis acids, $TiCl_4$ and $SnCl_4$, in this study. Nonyl aldehyde was used as it was the substrate most studied [28] before. Results are shown in table 3.1 for the synthesis of the homoallylalcohol 1-dodecen-4-ol, $CH_3(CH_2)_7CH(OH)CH_2CH{=}CH_2$ (**P1**).



P1

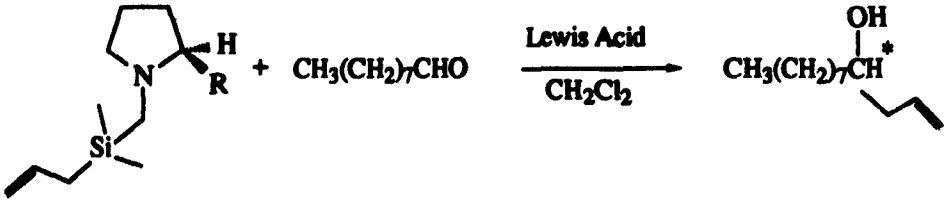
Table 3.1 Results from the synthesis of 1-dodecen-4-ol



Entry	R	Lewis acids	Equiv.	T (°C)	Time (hrs)	Yield (%)	ee (%)		Abs. conf.
							$[\alpha]_D^a$	CGC[b]	
1	$-CH_2O(CH_2)_2OCH_3$ (S1)	$TiCl_4$	3	-50	20	67	4.8	5.4	S
2		"	"	-78	28	25	12.4	12.5	"
3		"	1	-78	29	<5			"
4		$SnCl_4$	3	-50	20	50	3	4.5	"
5		"	"	-78	26	37.4	4.7	5	"
6		"	1	-78	26	18		8	"
7	$-CH_2OH$ [c] (S2)	$TiCl_4$	3	-50	20	67	5	10	"
8[d]		"	"	"	"	70	22	20.5	"
9		"	"	-78	"	60	5.1	4	"

a) The ee was determine by $\alpha_{[D]}$ method, base on the referenced value of 10.7° for the alcohol with R absolute configuration [40]. b) The ee was determined by gas chromatography using Chiraldex G-TA ™ column. c) Substrate prepared by R. Horvarth [41]. d) Procedure B of homoallylic alcohol synthesis was applied for this entry only.

Table 3.1 Results from the synthesis of 1-dodecen-4-ol



Entry	R	Lewis acids	Equiv.	T (°C)	Time (hrs)	Yield (%)	ee (%)		Abs. conf.
							$[\alpha]_D$[a]	CGC[b]	
1	$-CH_2O(CH_2)_2OCH_3$ (S1)	$TiCl_4$	3	-50	20	67	4.8	5.4	S
2		"	"	-78	28	25	12.4	12.5	"
3		"	1	-78	29	<5			"
4		$SnCl_4$	3	-50	20	50	3	4.5	"
5		"	"	-78	26	37.4	4.7	5	"
6		"	1	-78	26	18		8	"
7	$-CH_2OH$ [c] (S2)	$TiCl_4$	3	-50	20	67	5	10	"
8[d]		"	"	"	"	70	22	20.5	"
9		"	"	-78	"	60	5.1	4	"

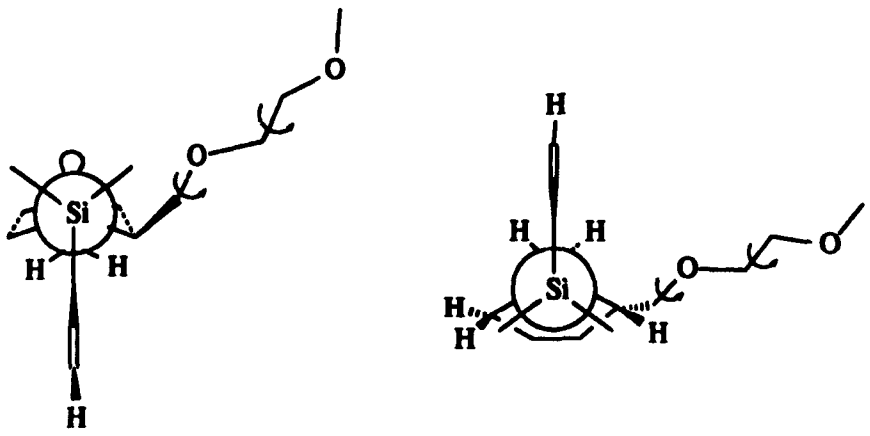
a) The ee was determine by $\alpha_{[D]}$ method, base on the referenced value of 10.7° for the alcohol with R absolute configuration[40]. b) The ee was determined by gas chromatography using Chiraldex G-TA ™ column. c) Substrate prepared by R. Horvarth[41]. d) Procedure B of homoallylic alcohol synthesis was applied for this entry only.

There are three major observations from these results. First, compare to **A10 - A12, S1** which has one more coordination site and was expected to form better chelated complex with LA:RCHO, the chemical yield (best case scenario, entry 1, Table 3.1) is comparable but the ee was markedly lower, under the same reaction conditions.

Secondly, as the temperature was lowered, there was an increase in ee. This is understood as the temperature affects the kinetics of the reaction. Therefore selectivity would be enhanced at lower temperature because it is kinetically controlled. And finally, the same effect from lowering the amount of Lewis acid to one equivalent was seen for all substrates. The chemical yield of the reaction was almost insignificant, down to less than 5%.

Let us consider first **S1** which has two coordinating sites from the two ethereal oxygens, aside from the tertiary nitrogen of the pyrrolidine ring. The most stable conformation of **S1**, calculated by MMX program, is shown by **C1** (Scheme 3.1). This conformation is more stable than **C2** although it has the CH_2 eclipsing with the nitrogen substituent, avoiding jamming the two silyl methyl group in to the pyrrolidine ring.

Scheme 3.1 Stable conformation of 2,2-Dimethyl-1-{1-[(S)-2-(2-methoxy-ethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (S1)



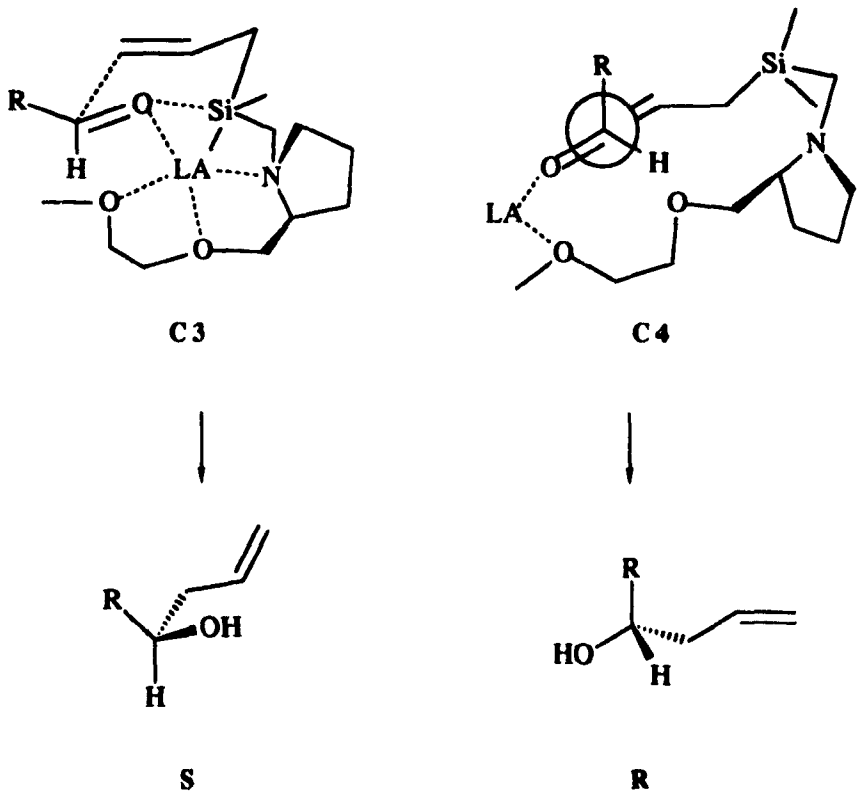
C1 C2

bonds rotate to chelate with Lewis acid

It is expected that chiral auxiliary induced asymmetric allylation of the aldehyde would result through Lewis acid/Lewis base chelated complex. The Lewis base coordinating sites are the two oxygens and the nitrogen as mentioned above. These sites, with their chiral property, upon chelating with the aldehyde-Lewis acid complex would make the nucleophilic attack to one face of the carbonyl more selective than the other. Since the reactions were carried out in CH_2Cl_2, a non coordinating solvent, interference with the chelated complex by the solvent won't be a factor in the outcome. Proposed transition states for the allylation based on molecular model, satisfying steric demand, are shown in scheme 3.2. As previous studies have shown that both anti-periplanar and syn-clinal transition states are possible, the results here will dictate the one that most likely took place. The long chelating chain of the allylsilane moiety made both model possible, as

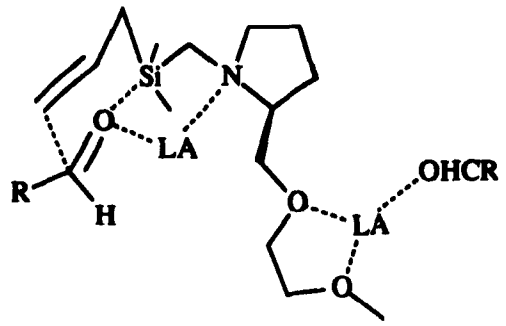
shown, with Lewis acid coordinating. Consistent results of absolute stereo configuration (S) shows an overall syn-clinal preference.

Scheme 3.2 Proposed transition state models for the synthesis of 1-dodecen-4-ol



Starting from C1, in order to form the chelate with one molecule of Lewis acid in C3 (Scheme 3.2), at least two bonds had to be rotated as indicated (scheme 3.1). Measurements calculated by MMX show that, if the nitrogen were replaced by the carbon atom on the pyrrolidine ring, the dihedral angle CH-CH-CH_2-O (64°) is 10° less than that of N-CH-CH_2-O (74°) in the stable conformation. This implied that there is a repulsion between the nitrogen's lone pair of electrons and that of the pyrrolidinemethanol's oxygen

(or, in other word, there is a tendency of the oxygen to stay away from the nitrogen). This presents an alternative possibility at higher Lewis acid concentration, as shown by C5.



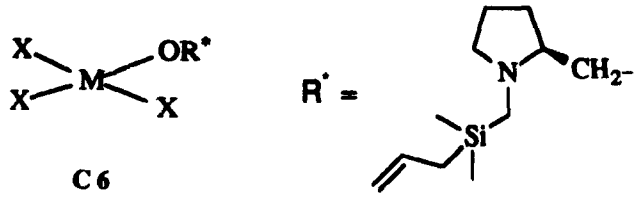
C5

As Lewis bases, ethers are found relatively weak and form fragile complex with Lewis acids. The tertiary alkyl amines, due to its steric bulk, do not form strong complex either [42]. Therefore chelating effect in the case of C3 is relatively weak to strongly favor the syn-clinal over the anti-periplanar transition state, as in C4. This may account for the poor stereoselectivity in the reaction.

These results pointed to a better chelating candidate to favor a syn-clinal transition state, ie., better controlling of the homoallylic alcohol synthesis. These includes functional groups such as carbonyl (esters, ketones, aldehydes) and amides which are much better donor, Lewis bases, than ethers [42]. Such may be the case as shown by the enhanced stereoselectivity results from using **A10**, **A11** and **A12**.

When **S2** was used as the allyl moiety, interesting results were observed. If the Lewis acid was allowed to complex with the aldehyde first, as normally done in homoallylic alcohol synthesis (procedure A), the ee was low (entries 7 and 9, Table 3.1). But when **S2** was added first and reacted with the Lewis acid before the aldehyde could be

complexed (procedure B), an increase of 17% (from 5% to 22%) in ee was observed. In this case, the in-situ-formed chiral Lewis acid **C6** is acting as a catalyst and an allyl moiety simultaneously. However, there were instances where this type of Lewis acid ($MX_{n-1}OR^*$) were found be inefficient catalyst [43]. This is due to partial redistribution of the



C6

chiral ligand [10e] as shown by reaction 3.1, to give MX_n which is a stronger Lewis acid and thus competes efficiently with $MX_{n-1}OR^*$ for the Lewis base. This could be the reason why **S2** still yielded a lower ee than **A12** in the synthesis of 1-dodecen-4-ol.

$$2\ MX_{n-1}OR^* \rightleftharpoons MX_{n-2}(OR^*)_2 + MX_n \qquad \text{(Reaction 3.1)}$$

The fact that **A12** yielded a better ee than **S2** also shows that the first oxygen (of the S-2-pyrrolidinemethanol backbone) is important for chelating and stereoselectivity control. It also suggested that steric bulk from the methoxyethoxy chain may have played a more important role than expected. The tertiary nitrogen, quite bulky itself, might not have coordinated with the LA:RCHO complex, as expected. In such a case, the second oxygen (methoxy) was more available for coordination. This caused the chiral center and the coordinating site to be farther from the reaction center. Therefore, the chiral auxiliary was not efficient in inducing asymmetric synthesis.

Titanium tetrachloride seemed to be a better catalyzing and chelating Lewis acid than $SnCl_4$, in terms of chemical yield and stereoselectivity. This could be due to the fact that,

complexing ligand with $SnCl_4$ isomerises easier than with $TiCl_4$ [13], losing its structural stability, hence, selectivity.

Chelation induced asymmetric synthesis is possible when the ratio of LA:RCHO:allylsilane is 1:1:1. If excess of Lewis acid was used, intramolecular chelation would be disrupted, as mentioned above. Denmark [27] has found that a 1:1 $SnCl_4$:RCHO complex favors a syn transition state. Therefore, one could expect one equivalent of Lewis acid to be optimum. However, it is not clear why the chemical yield was so low when this ratio of Lewis acid was used. One possible reason is that, the Lewis acid would preferably form a LA.2RCHO complex and became too hindered for allylation at low temperature. This, therefore, would not favor C3 as the transition state. Thus, the optimum ratio of Lewis acid to aldehyde was about 3 for this substrate system.

CONCLUSIONS

Chelating effect between the chiral allyl moiety and the LA did favor the syn-clinal, though modestly due to weak chelating and steric hindrance, in the synthesis of the homoallylic alcohol, 1-dodecen-4-ol. The introduction of a second oxygen chelating site therefore has had a negative effect on stereochemical control of the reaction.

Further studies should involve finding a better coordinating ligand. Bidentate (or multidentate) Lewis acids can be considered now that there is more and more reports on their syntheses and synthetic utility [10b,e]. And if prolinol derivatives are to be used, the coordination site should not be farther than the prolinol oxygen position.

EXPERIMENTAL SECTION

General Methods. Materials were obtained from commercial suppliers unless noted otherwise. Reaction solvents were all dried distilled. Distilled hexanes was used for column chromatography. Other solvents were reagent grade or better. Whenever is mentioned, water means distilled water. Analytical thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254}. Ninhydrin/ethanol or ceric acid mist was used for compound visualization. Flash chromatography analysis was done on Merck silica gel 60 (230 - 400 mesh ASTM). Capillary gas chromatography analysis was performed on a Hewlett Packard 5890A and 5890 Series II instruments fitted with a 25m x 0.2mm high performance column (cross-linked methylsilicon, film thickness of 0.33μm). Chiral GC measurements were carried out on the *Chiraldex G-TA* ™ (γ-cyclodextrin, trifluoroacetyl) 30m x 0.25mm [44] . Optical rotations were determined on the JASCO DIP-140 digital polarimeter. Infrared (IR) spectra were recorded on an Analect FT, AQS-18 spectrophotometer with a MAP-67 data system and are reported in reciprocal centimeters (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian, XL-200, XL-300 or JEOL-270 instruments. All NMR spectra were done with $CDCl_3$ as the solvent and internal standard. Chemical shifts are expressed in part per million (ppm). Significant ^{1}H NMR data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), number of proton and coupling constant in Hertz (Hz). Decoupling, DEPT, HETCOR, and COSY experiments were performed to unambiguously assign selected spectra. Low and high resolution mass spectra (MS) were obtained with Du Pont 21-492B and ZAB 2F HS mass spectrometer (EI, 70eV; CI, H^{+}) and are reported as m/e (relative intensity in percent). "Standard work-up" will refer to: treatment of the reaction mixture with brine; extraction of the aqueous phase with diethyl ether; drying the organic extract over magnesium sulfate; concentrating the extract with a rotary evaporator and removal of volatile impurities under high vacuum.

General Procedure for O-alkylation of N-protected L-prolinol. The N-protected S-2-prolinol was added into the pre-washed (by hexanes, THF) sodium hydride (NaH) in THF at 0°C, stirred for 15 minutes, and the electrophile was added dropwise. The mixture solution was kept stirring at 0°C for 15 min then gradually warmed up to room temperature (0.5 hour) and to reflux (70-80°C, 2hrs - overnight). After cooling down to room temperature, the solids were filtered and washed by ethyl acetate. The filtrate was evaporated to dryness to give the crude product. Purification was carried out by flash chromatography, using CH_2Cl_2:MeOH (9:1) as eluting solvent.

2-Iodoethyl methyl ether (B2) [37]. In a solution of acetone (25ml) was added NaI (5.175g, 54.7mmol) at room temperature. 2-Chloroethyl methyl ether was then added in dropwise, the mixture was then stirred and refluxed over night. After the reaction was over, the mixture was cooled down to room temperature and poured in to 15ml of ice water. The product was extracted with ether, the combined organic phase then washed by 10% aq. $Na_2S_2O_3$, water and brine. The organic phase then was dried over $CaCl_2$, distilled at ambient atmosphere to remove ether and under reduced pressure to collect the product 2-iodoethyl methyl ether, bp 76-80°C/90 mmHg, in 87% yield (8.85g). ^1H NMR (200 MHz, $CDCl_3$) δ 3.3 (s, 3H), 3.16 (t, 2H, J=6.5 Hz), 3.55 (t, 2H, J=6.5 Hz).

(S)-1-(2-Methoxyethyl)-2-hydroxymethylpyrrolidine (B3). ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 - 1.95 (m, 4H), 2.5 (td, 1H, J=9, 8 Hz), 2.69 (dt, 1H, J=13.8, 5.1 Hz), 2.9 (m, 1H), 3.09 (dt, 1H, J=13.8, 5.9 Hz), 3.3 (m, 1H), 3.45 - 3.7 (m, 4H), 4 (bs, 1H, alcoholic); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.8, 27, 55, 55.5, 58.9, 61.8, 67.5, 69.9; IR ($CHCl_3$) 3420, 2980, 3025, 2900, 2830, 1452, 1376, 1116 cm^{-1}; MS (EI) *m/z* 128 (100), 114 (40), 110 (27), 70 (21), 59 (18), 129 (10), 82 (9), 96 (9), 155 (5).

S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (B4) [38]. Compound **B14** (0.5573g, 3mmol) was stirred in 2ml of 20% aq. KOH solution at room temperature for overnight. Potassium carbonate (K_2CO_3) was then added into the reaction mixture untill saturation was reached. The solution was then filtered, the filtrate extracted with ethyl acetate, and the organic phase washed with brine, dried over $MgSO_4$. The solvent was then removed under reduced pressure to give 0.4478g of the spectrally-clean product C4 in 95% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 3.34 (s, 3H), 3.4 - 3.6 (m, 4H), 3.2 - 3.5 (m, 3H), 1.6 - 1.9 (m, 3H), 1.28 - 1.3 (m, 1H), 2.75 - 3 (m, 2H), 2.1 - 3.1 (s, 1H, varies); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.2, 27.9, 46.5, 57.9, 59, 70.6, 72.1, 75.2; IR ($CHCl_3$) 665, 736, 770, 794, 1095, 1206, 1242, 1457, 1625, 2372, 2872, 2928 cm^{-1}; MS (EI) *m/z* 70 (100), 71 (23), 55 (15), 43 (14), 59 (12), 84 (11), 128 (9); $[\alpha]_D^{20}$ -11° (c=1.759, CH_2Cl_2).

(S)-1-Benzyl-2-hydroxymethylpyrrolidine (B5) [30]. Benzylchloride (2.4ml, 20.8mmol) was added dropwise into L-prolinol (1.05g, 10.4mmol, in 10ml THF, 15°C) and the mixture was stirred overnight. Sodium carbonate anhydrous (1.07g in 10ml of water) was added into the reaction solution, and the mixture was stirred until all solid dissovled. The reaction mixture was extracted into chloroform, the combined organic layers washed with water, brine, dried over $MgSO_4$ and rotatory evaporated to give the crude product which was purified by flash chromatography (hexanes:ethyl acetate 7:3) to give 0.923g (46.3%) of the pure (S)-1-Benzyl-2-hydroxymethylpyrrolidine: ^1H NMR (200 MHz, $CDCl_3$) δ 1.63 - 2.04 (m, 4H), 2.35 (m, 1H), 2.82 (m, 1H), 3.02 (m, 1H), 3.4 (b, alcoholic), 3.43 and 4 (d, 2H, J=12.2 Hz), 3.47 and 3.66 (dd, 2H, J=10.7, 3.6 Hz), 7.28 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 54.3, 58.6, 61.7, 64.7, 127.3, 128.4, 129, 138.1.

(S)-1-Carbobenzoxy-2-hydroxymethylpyrrolidine (B6) [32]. A mixture of **B1** (5.06g, 50mmol) and K_2CO_3 (16.53g, 120mmol) was stirred vigorously in CH_3CN at room temperature for 15 min. The solution was then cooled down to -20°C, benzyl chloroformate (9.38g, 55mmol, in 10ml of CH_3CN) was added dropwise, and the mixture stirred for 2hrs at that temperature. Water was then added and the reaction solution extracted with $CHCl_3$. The organic layers were combined and washed with water, aq. HCl 5%, rinsed with water, brine and dried over $MgSO_4$. Rotary evaporation gave a very vicous oil of the crude product which after purification by flash chromatography (hexanes:ethyl acetate 1:1) gave 10g (85%) of the pure product **B6**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.5 - 2.1 (m, 4H), 2.5 (varies, bs, 1H, alcoholic), 3.3 - 3.7 (m, 4H), 4.0 (m, 1H), 5.14 (s, 2H), 7.35 (m, 5H, aromatic).

(S)-1-Carbobenzoxy-2-[(2-methoxyethoxy)methyl]pyrrolidine (B7). General procedure for O-alkylation, from **B6** and **B2** (2.2%). ^1H NMR (200 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.3 - 3.7 (m, 8H), 4 (m, 1H), 1.76 - 2.02 (m, 4H), (s, 2H), 7.36 (m, 5H, aromatic). Side products from the synthesis of **B7** : **2-Methoxyethyl benzyl ether (B8)**, 27% yield, ^1H NMR (200 MHz, $CDCl_3$) δ 3.4 (s, 3H), 3.6 (m, 4H), 4.7 (s, 2H), 7.38 (m, 5H); **[3.3.0]-1-Aza-3-oxabicyclooctane-2-oxide (B9)**, 10% yield, ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 - 1.55 (m, 1H), 1.78 - 2.15 (3H), 3.11 (m, 1H), 3.62 (m, 1H), 3.8 - 3.95 (m, 1H), 4.15 (dd, J=9, 3.4 Hz, 1H), 4.48 (dd, J=9, 7.6 Hz, 1H).

[3.3.0]-1-Aza-2-thia-3-oxabicyclooctane-2-dioxide (B10) [35] . To a stirred mixture of L-prolinol (2.03g, 20mmol) and triethylamine (6ml, 43mmol) in dichloromethane (120ml), at -78°C was added dropwise a solution of sulphuryl chloride (1.8ml, 18.5mmol) in CH_2Cl_2 (120ml). The mixture was stirred at -78°C for 3hrs, gradually brought up to room temperature and stirred for an hour. The reaction mixture

was then washed with aq. HCl 1N (3x30ml), brine (2x30ml), dried over $MgSO_4$ and the solvent evaporatively removed. Purified by flash chromatography (pentane:ether gradient) to give the desired product which must be recrystallised from ether to give 0.794g of the pure product. The dimerised product **B11** came out of the column precipitating and weighed 0.185g. The ratio of the monomer and the dimer was 9 : 1, for a combined yield of 30%: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.75 - 2.35 (m, 4H), 3.28 (dt, 1H, J=12, 7 Hz), 3.7 (dt 1H, J=12, 6 Hz,), 4.05 (dd, 1H, J=8, 6 Hz), 4.28 (m, 1H), 4.55 (dd, 1H, J=9, 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25, 31.2, 51, 62.4, 71.9; MS *m/z* calc'd for $C_5H_9NO_3SH^+$: 164.0381, found 164.0381. **[6.3.3]-1,9-Diaza-2,7-dithia-3,11-dioxatricyclohexadecane-2,7-tetraoxide (B11)** : Dimerised side product from the synthesis of **C10**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (m, 2H), 1.97 (m, 4H), 2.22 (m, 2H), 3.45 (dt, 2H, J=9.8, 6.7 Hz), 3.77 (dt, 2H, J=9.9, 6.8 Hz), 4.05 (dd, 2H, J=11.2, 6 Hz), 4.13 (dm, 1H, J=1.7 Hz), 4.39 (dd, 2H, J=11.2, 1.7 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.8, 28.8, 51.3, 58.9, 72; IR (KBr) 760, 890, 1170, 1290 cm^{-1}; MS *m/e* calc'd for $C_{10}H_{18}N_2O_6S_2H^+$: (MH^+) 327.0684, found 327.0685.

(S)-1-Formyl-2-hydroxymethylpyrrolidine (B12) [36] . A neat mixture of L-prolinol (10.24g, 97.7mmol) and ethylformate (9.8ml, 121mmol) was stirred overnight at 0°C. Without working up, the mixture was evaporated (to remove the ethanol that had been formed) to give the crude product which was purified by flash chromatography (CH_2Cl_2 : MeOH 9:1) to give 12.63g (97%) of pure **B12**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 - 2.3 (m, 4H), 3.2 - 3.75 (m, 4H), 3.75 - 4.1 (m, 1H, two conformers), 4.92 (d, 1H, J=8 Hz, OH), 8.21 and 8.25 (s, 1H, aldehydic, two conformers); $[\alpha]_D^{20}$ - 44° (c=0.2036, benzene).

2-Methoxyethyl tosylate (B13). To a solution of tosylate chloride (2.1757g, 11.4mmol) in pyridine (5ml), was added 2-methoxy ethanol dropwise and the whole mixture was stirred overnight at room temperature. After the reaction was finished,

working up was carried out by filtering the white pyridinium salt and the solid washed by ether. The filtrate was collected and extracted with aq. HCl 1N solution (6x10ml), washed with brine and dried over $MgSO_4$. Evaporatively removal of the solvent gave spectrally-clean product **B13** (2.08g, 95%): ^1H NMR (200 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.56 (t, 2H, J=4.8 Hz), 4.16 (t, 2H, J=4.8 Hz), 7.32 (d, 2H, J=8.4 Hz), 7.78 (d, 2H, J=8.4 Hz).

(S)-1-Formyl-2-[(2-methoxyethoxy)methyl]pyrrolidine (B14)[38]. A solution of (S)-1-Formyl-2-hydroxymethylpyrrolidine (**C12**) (50mmol, 6.483g/100ml THF) was added dropwise into a solution of NaH (60mmol, 1.445g/100ml THF) at 0°C. The slurry was stirred at 0°C for 30 min, then a solution of **B13** (60.8mmol, 14.05g/25ml DMF) was added in dropwise. The mixture was gradually warmed up to room temperature (30 min) then refluxed at 50-60°C for 2 hours. After refluxing, the reaction mixture was cooled down to room temperature and filtered off solid residues. Removing the solvents under high vaccum gave 10g of the crude product which was purified by flash chromatography (CH_2Cl_2:CH_3OH 9:1) to give 7.30g of pure **B14** : ^1H NMR (300 MHz, $CDCl_3$) δ 1.6 - 2 (m, 4H), 3.3 (s, 3H), 3.3 - 3.63 (m, 8H), two multiplets - two conformers of 1H : 3.88 - 3.98 and 4.05 - 4.14, two conformers : 8.17 and 8.28 (s, 1H, aldehyde); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.8, 73.9, two conformers : 22.6 and 23.6, 27.6 and 27.7, 46.8 and 43.5, 54.5 and 56.7, 58.9 and 59, 70.4 and 70.6, 160.5 and 161.1; IR ($CHCl_3$) 670, 794, 1105, 1205, 1223, 1386, 1656, 2376, 2875, 3000 cm^{-1}; MS (EI) *m/z* 98 (100), 70 (47), 111 (45), 112 (10), 99 (10), 187 (2), 43 (4).

2,2-Dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (S1). A neat mixture of S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (**B4**) (2.21g, 13.9mmol) and allylchloromethyldimethylsilane (1.15g, 6.95mmol) was refluxed for 2hrs at 90-110°C in the presence of catalytic amount of NaI (0.3g) and molecular sieves (3Å, 0.5g). After cooling down to room temperature, the reaction mixture was subjected to standard work-up procedure to give 1.98g of the crude product.

Purifying by flash chromatography (hexanes:ethyl acetate 4:1) gave 1.72g (90%) of the pure product **S1**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.45 - 3.63 (m, 4H), 3.3 and 3.5 (dd, J=10.9, 7.3 Hz, 2H), 2.42 (m, 1H), 1.55 - 1.95 (m, 4H), 3.05 and 2.12 (m, 2H), 1.77 and 2.5 (d, J=14 Hz, 2H), 0.024 and 0.041 (s, 6H), 1.54 (d, J=8.1 Hz, 2H), 5.65 - 5.88 (m, J_{trans}=15.7 Hz, J_{cis}=11.4 Hz, J_{12-13}=8.1 Hz, 1H), 4.81 (ddd, J=15.7, 11.4 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -3.5, 23, 23.3, 45, 58, 58.9, 67.2, 71, 72, 75, 112.5, 134.5; IR ($CHCl_3$) 847, 891, 1113, 1249, 1450, 1615, 2335, 2880, 2950 cm^{-1}; MS (EI) *m/z* 182 (100), 183 (18), 172 (13), 59 (12), 184 (5), 85 (4); $[\alpha]_D^{20}$: -62° (c=0.462, benzene). MS *m/e* calc'd for $C_{14}H_{29}NO_2SiH^+$: (MH^+) 272.2047, found 272.2046.

General procedure for the homoallylic alcohol synthesis

Procedure A. To a solution of the aldehyde (1.45mmol) in CH_2Cl_2 (10ml) was added the Lewis acid (1M/CH_2Cl_2) and the mixture stirred for 15 min. The allyl silane solution in CH_2Cl_2 (1.8mmol, 1M) was then added dropwise, and the mixture was allowed to react at the specific temperature and time.

Procedure B. A mixture of the allyl silane (1.33mmol) and the Lewis acid (3.9mmol, 1M/CH_2Cl_2) in CH_2Cl_2 (10ml) was stirred at -50°C for one hour. The neat aldehyde (1.2mmol) was then added and the mixture was stirred for a specific time.

Working up. Aqueous solution of sodium bicarbonate saturated (aq. $NaHCO_3$ sat., 5ml) was added into the reaction solution at the reacting temperature. The solution then gradually warmed up to room temperature and extracted with ether. The combined organic layers was then washed with brine, dried over $MgSO_4$ and the solvent removed evaporatively to give the crude homoallylic alcohol product which was purified by regular chromatography using hexanes:ethyl acetate 100:1 as eluting solvent.

1-Dodecen-4-ol (P1) [28]. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.8 (t, 3H, J=7.4 Hz), 1.3 - 1.5 (broad, 12H), 1.45 (broad, 2H), 1.7 (broad, 1H, alcoholic), 2.1 (ddt, 1H, J=13.5, 8.6, 8.1 Hz), 2.3 (ddd, 1H, J=13.5, 8.1, 4.3 Hz), 3.75 (ddm, 1H, J=13.5, 8.1 Hz), 5.12 (dd, 2H, J=14.7, 0.3 Hz), 5.8 (dm, 1H, J=8.1 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14, 22.6, 25.6, 29.2, 29.55, 29.6, 31.9, 36.8, 41.9, 70.7, 118,134.9.

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44. The derivatised alcohol was prepared with trifluoroacetic anhydride to be used on the GC, following reported procedure by D. W. Armstrong et al., *J. Chromatogr.* **1990,** *509,* 303.

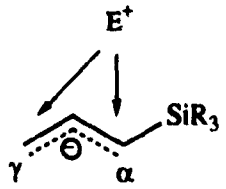
PART 2

Chapter 4. ELECTROPHILIC ALKYLATION

I.1 INTRODUCTION

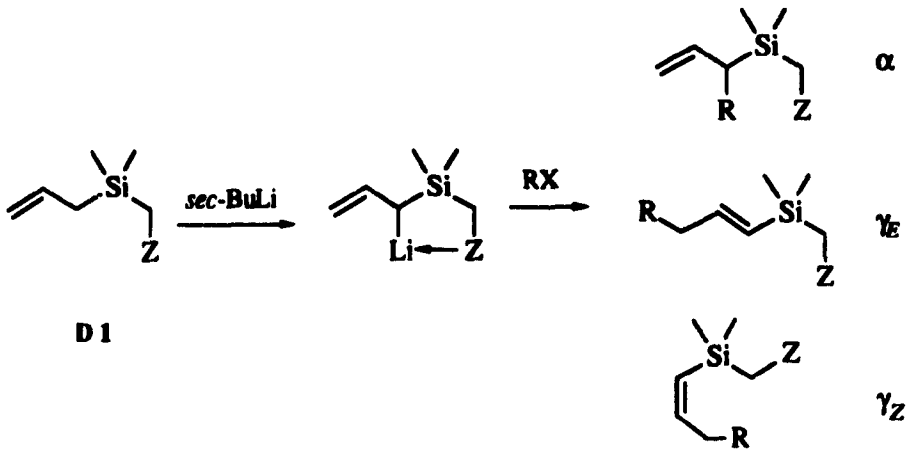
The chemistry of α-silylallyl carbanion is attracting increasing attention due to its potential usefulness in organic synthesis. The anion is readily generated by several established methodologies [1]. The reversible polarity (umpolung) anion can be attacked by an electrophile at either end, γ or α position (Scheme 4.1).

Scheme 4.1 Possible electrophilic attack sites on silylallyl anion



Original work by Corriu [2] has shown that lithiated allylsilane generally favor γ-electrophilic substitution. The regiochemical control in electrophilic alkylation reaction of allylsilane was investigated in depth by Chan's group (Scheme 4.2) [3-5]. It was found that chelation between Li^+ and the ligand substituent on silicon promoted α-selectivity. Factors affecting the chelated complex, hence regiochemical control, including solvent, steric and electronic effect were considered. Following is a relevant summary of the results from Horvath's studies and others related works [6].

Scheme 1.2 General electrophilic alkylation with chelating effect [4]



D1

I.2 STRUCTURE OF LITHIATED ALLYLIC COMPOUNDS

Lithiated allyl anion exists in three possible forms as shown in scheme 4.3 where D2 is favored in ether [7] and D4 in hydrocarbon solvents . Studies by NMR show that at low temperature fluxional behavior of D4 can be limited [8].

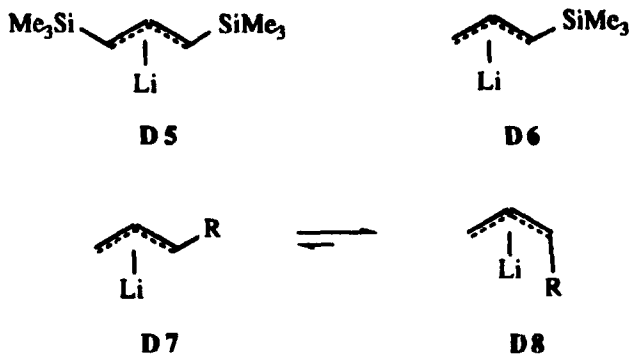
Scheme 4.3 Resonance structures of lithiated allyl anion [8]

ionic π-bonded fluxional

D2 D3 D4

Silylallyl anion and disilylallyl anion strongly favor the exo conformation **D5** and **D6** respectively [9]. On the other hand, alkyl anion equilibrates between exo **D7** and the more favored endo structure **D8** (Scheme 4.4) [9].

Scheme 4.4 Structural comparison between alkyl- and silyl-allyl anion lithium complex [9]



D5 **D6**

D7 **D8**

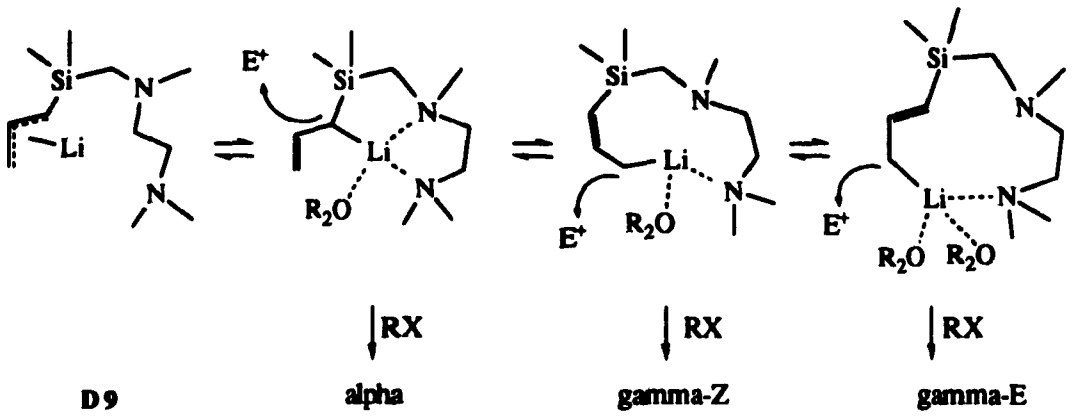
I.3 COORDINATING EFFECT

Lithium at the oxidation state of +1 can have a maximum of 4 coordination number. Organolithium compounds tend to aggregate in solution. They could be deaggregated by Lewis base which could be solvent or other coordinating molecules[10]. Coordination by Lewis base with lithium also increases the polarization of the carbon-lithium bonds [11], i.e., increases charge density at the carbon end. The electrophilic attack at the carbon center is thus enhanced.

Internal coordination also stabilizes the Li-C bond and slows down the fluxional behavior of the silylallyl anion lithium complex. It was therefore suggested that [4], for example, there are three possible electrophilic attack sites in the equilibrating structures of **D9** as shown in scheme 4.5. Attacking at each lithiated site by an electrophile will result in

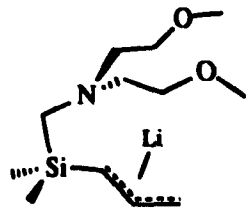
α, γ_E or γ_Z substituted product. The same phenomenon has also been suggested by others [12].

Scheme 4.5 Possible coordinating conformers of lithiated allylsilane in a coordinating solvent [4]

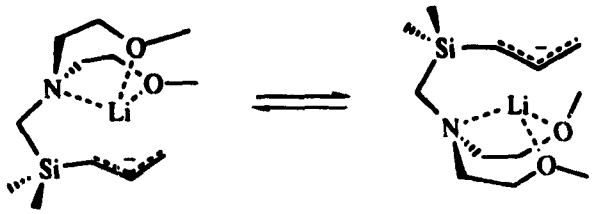


Further NMR studies by Fraenkel [9] shows the structure of **D10** in a non coordinating solvent toluene as shown in scheme 4.6, with maximum chelation (tridentate). Therefore, well controlled coordination could result in enhanced regioselectivity to favor α substitution, and at the same time, enhances chemical reactivity of the allyl anion.

Scheme 4.6 Lithiated silylallyl anion in non-coordinating solvent [9]



D10



D11 **D12**

I.4 SOLVENT EFFECT

As regioselectivity can be controlled by chelating effect, good electron donating solvents which can coordinate with Li will disrupt the chelated complex. This will therefore result in a loss of regioselectivity. For example [4], upon changing from ether to tetrahydrofuran (THF), α selectivity decreased from 100% to 87% for alkylation of **D10** using hexyl iodide. This is not surprising since THF is a better coordinating Lewis base than ether [15] due to its smaller molecular size. THF is therefore much more effective in disrupting the internal chelated complex between Li and the allylsilane ligand. The same solvent effect on chelation and regioselectivity has also been observed in other substrate systems [13, 14].

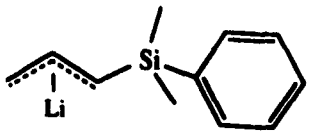
I.5 STERIC EFFECT

Generally, large bulky alkyl halide electrophiles result in a decrease in α and increase in γ substitution [4, 13, 14]. Large conjugate base, such as *n*-BuLi/t-BuOK, also

resulted in an improve of γ selectivity. Bulky substituent on silicon also favors γ attack by electrophiles [14].

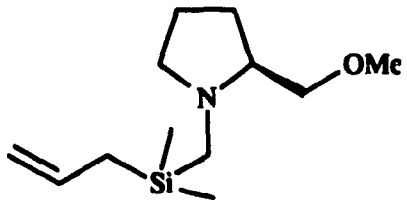
I.6 ELECTRONIC EFFECT

Favorable orbital interaction from the silicon substituted phenyl **D14** was thought to cause α-selective substitution by methyl iodide [16]. Allylic substituent with prominent electron donor or acceptor properties could change the charge density distribution on the allyl anion lithium complex. Therefore the regioselectivity of alkylation would be altered in comparison with unsubstituted allyl [17].

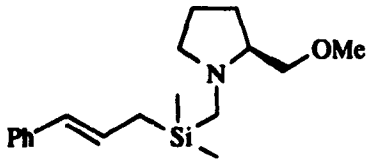


D14

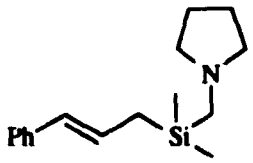
Using various allylsilanes with coordinating silicon substituent (**D1**, scheme 4.2), Horvath and Chan [4] were able to study the effect of chelation on the regiochemical control of the electrophilic alkylation. In general, it was found that, α-alkylation is favored, due to coordination that binds Li in the α position, with unhindered alkyl halide (eg., MeI) and in weak coordinating solvent system (eg., ether). Using allylsilane with a chiral coordinating silicon substituent (**D15**), almost 100% diastereoselectivity was achieved. Later on, Lamothe and Chan [13], using substituted allylsilane **D16**, also found that the best α-selectivity was obtained in a non-coordinating solvent (toluene). They also observed essentially the same α to γ product ratio from **D17** and **D18** in THF, which implied that the nitrogen of the pyrrolidine ring was not significantly influencing the regioselective alkylation by chelating with Li.



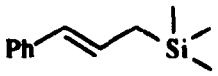
D15



D16



D17

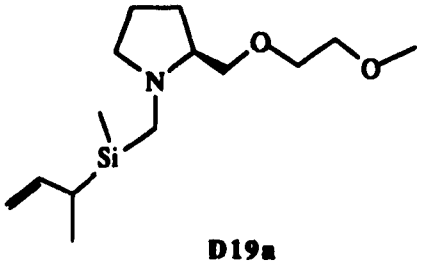


D18

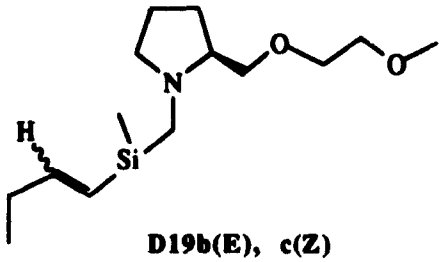
This project will continue to study the chiral chelating effect on the stereo- and regiochemical controlled electrophilic alkylation of unsubstituted allylic silane 2,2-dimethyl-1-{1-[(S)-2-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-4-pentene (**S1**) and 2,2-dimethyl-1-{1-[(S)-2-hydroxymethyl]pyrrolidinyl}-2-sila-4-pentene (**S2**), using *sec*-BuLi as the deprotonating agent and MeI and HexI as alkyl halide electrophiles. The steric and solvent effects will be looked at, in comparison with **D15** [4]. It was expected that with more chelating sites, better α regio- and stereochemical selectivity can be achieved.

II. RESULTS AND DISCUSSIONS

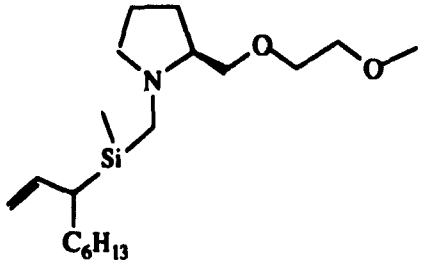
The results from the electrophilic alkylation of **S1** and **S2** are shown in table 4.1 in comparison with that of **D15** [4]. In general, chemical yields are relatively good.



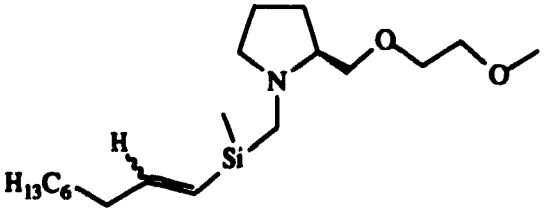
D19a



D19b(E), c(Z)

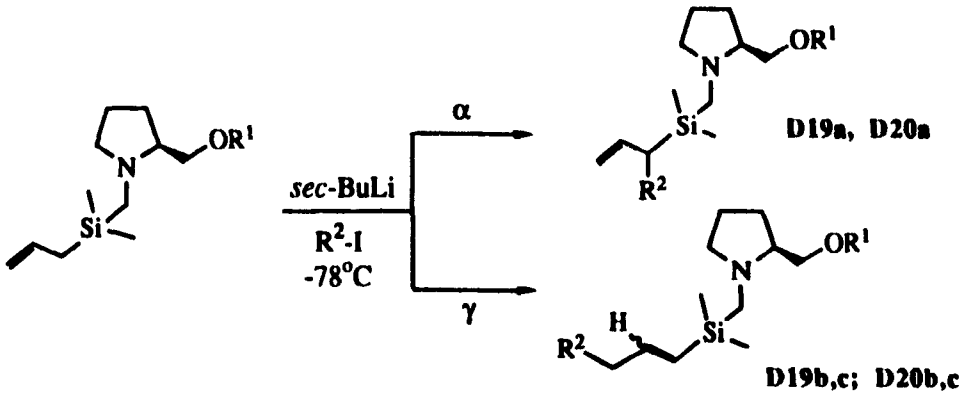


D20a



D20b(E), c(Z)

Table 4.1 Ratios and yields of products from electrophilic substitution of S1, S2 and D15



Entry	R^1	R^2	Solvent	Products	$\alpha : \gamma_E : \gamma_Z$	Yield (%)	ee (%) [b]
1	$(CH_2)_2OCH_3$ (S1)	CH_3	Ether	D19a:b:c	85 : 7 : 8	88 [i]	> 99
2		"	THF		68 : 18 : 4	98 [c]	"
3		n-Hex	Ether	D20a:b:c	43 : 52 : 5	85 [c]	"
4			THF		24 : 62 : 12	92 [c]	"
5	CH_3 [a] (D15)	CH_3	Ether		87 : 6 : 7	94 [c]	"
6			THF		85 : 0 : 15	69 [c]	"
7		n-Hex	Ether		63 : 34 : 3	66 [c]	"
8			THF		65 : 27 : 8	83 [c]	"
9	H (S2)	CH_3	ether		no reaction		
10			THF				
11		n-Hex	THF				

a) R. Horvarth's results [4]. b) determined by NMR, for the α-alkylated product. i) isolated yield. c) crude yield.

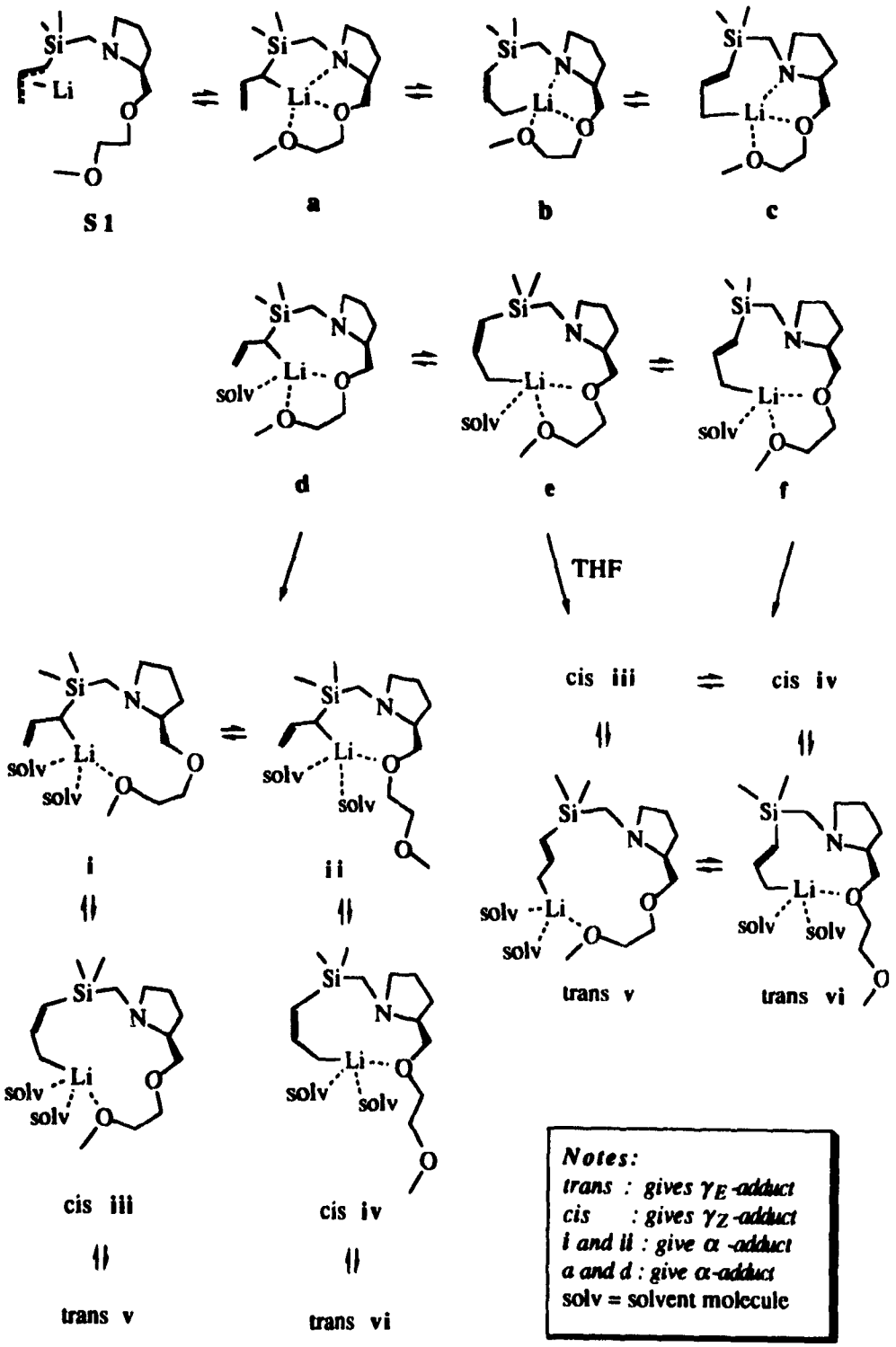
II.1 Regioselectivity

Chelation effect which resulted in α-selective methylation in ether and THF was observed with **S1** as was with **D15**. However, steric effect was more prominent with **S1** (entries 3 and 7, Table 4.1). It can be seen that, with the large electrophile HexI, there was a definite decrease in α adduct from **S1**. Changing from ether to THF as the solvent also had a bigger effect on the alkylation of **S1**, seen as a large decrease in α selectivity.

It is known that THF is a better coordinating molecule than ether. Thus it's understandable that THF would compete more efficiently with the allylsilane chelating ligand to form a coordination bond with Li. This disruption of the chelated complex intermediate would result in a loss of α selectivity. It is, therefore, intriguing as to why there seems to be less of a solvent effect on **D15**.

Proposed intermediate chelated complexes for **S1** and **D15** are shown in scheme 4.7 and 4.8 respectively. The tertiary nitrogen alone, as was shown by Lamothe and Chan [13], was not a strong influence in the chelate. This is probably due to its steric bulk and/or the unfavorable formation of the unsaturated heterocyclic 7-membered ring. Therefore the solvent molecules may have competed successfully with nitrogen for the Li coordination sites [18]. In such a case, **S1-d, e, f** (Scheme 4.7) and **D15-d, e, f** (Scheme 4.8) would be the effective chelated complex intermediates in a weak coordinating solvent, such as ether.

Scheme 4.7 Proposed chelated complex intermediates for S1

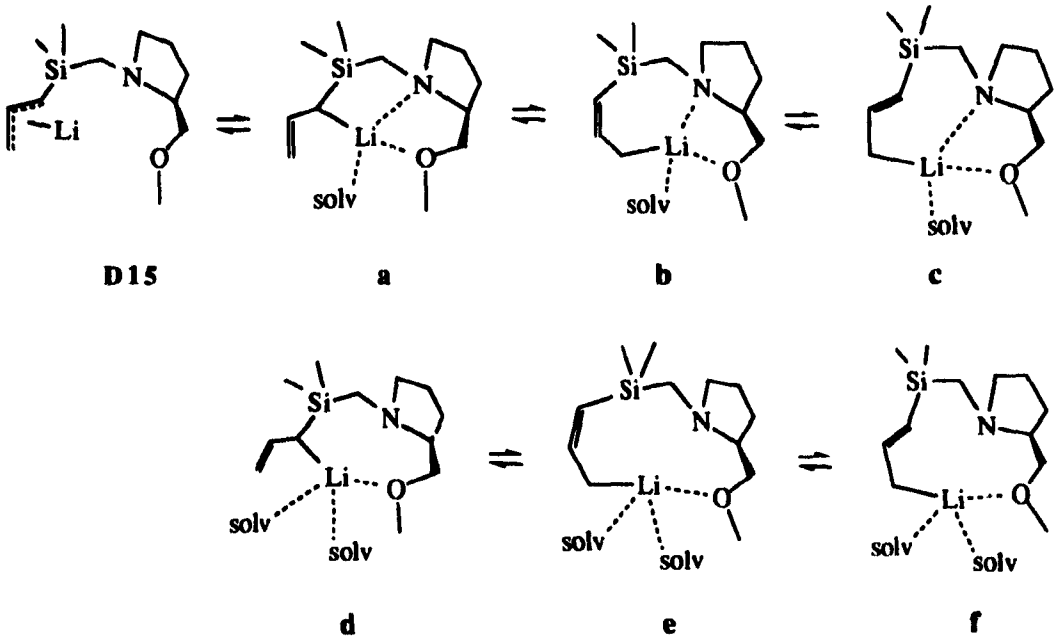


The large solvent effect in the methylation of **S1** shows that chelation did have influence on the regiocontrol of alkylation, since, having one more coordinating site in this case made the chelated complex become more solvent sensitive. Results in table 4.1 show that the regioselection (α:γ ratio) is the same for both **S1** and **D15** in ether. Thus, in weaker coordinating solvent such as ether, **S1d, e, f** and **S1a, b, c** would result in identical regiocontrol, when, on the average, a molecule of solvent will occupy a Li coordination site. However, upon changing to THF, one more oxygen coordination was replaced by a solvent molecule (results from stereoselectivity showed that Li must have coordinated with at least one oxygen atom, *vide infra*) and the solvent chelated intermediates then equilibrated to less strained larger rings (Scheme 4.7, **i - vi**). This equilibration resulted in a decrease in α and increase in γ adduct upon electrophilic attack by alkyl halide. As the unsaturated ring of the intermediate complex became larger (10 - 14-membered), the trans-complex prevailed over the cis-complex. Thus **v** (Scheme 2.1) would have the most influence since 14-membered ring is considerably less strained than a 10-membered one [19]. Therefore, solvent effect resulted in an increase in γ selectivity and at the same time favored the formation of the trans alkene (γ_E) product from **S1**.

This result from the electrophilic alkylation of **S1** can now help explain the peculiar observations from reaction with **D15** : the reduced solvent effect on regioselectivity, and a decrease in γ_E isomer for reactions carried out in THF. Thus as shown in scheme 4.8, a change in solvent donor ability would not change the conformation of the complex intermediate rings since the Li - O coordination bond would be intact. No significant change in the regioselectivity was anticipated as the solvent system was changed. In other word, having only one oxygen to coordinate with Li and with the consideration that nitrogen may not have participated in the chelation at all, **D15** can be said to be solvent-insensitive to regioselection. The only thing that was affected due to solvent change was the reactivity of the lithiated allyl anion. Being better as an electron donor, THF molecules

make the Li - C bond more polarized or increases charge density at the carbon end, and as discussed earlier, thus make the allyl anion more reactive. Electrophilic substitution by the alkyl halide then would become faster. At the same time, equilibrium between the cis (**D15e** - less ring-strained and more stable) to the strained unstable trans- **D15f** structure of the intermediate complex heterocycle was slower than the rate of substitution. The result was an increase in the Z isomer alkene adduct, with the extreme case being the total exclusion of the E isomer when the less bulky and hence more reactive MeI was the electrophile.

Scheme 4.8 Proposed chelated complex intermediates for D15



Note: solv = solvent molecule

With **S2** as the allylsilane, the electrophilic alkylation reaction did not yield any product. Moreover, upon quenching the reaction mixture with saturated aqueous NaCl, **S2** was recovered unchanged although the ratio of *sec*-BuLi to **S2** was 3 to 1. This suggested that deprotonation of the OH group was much more favorable, and that the hydroxyl hydrogen is more acidic than the allylic hydrogen. The lithium oxide and the excess *sec*-BuLi reagent probably formed aggregates and did not react further. Therefore, it is thought that, even if excess of sec-BuLi were used to ensure ionization of the allylic proton, the aggregatedly lithiated oxygen would not be able to participate in coordinating with the allyl anion-Li cation system to have regio- or stereochemical control effect.

II.2 Stereoselectivity

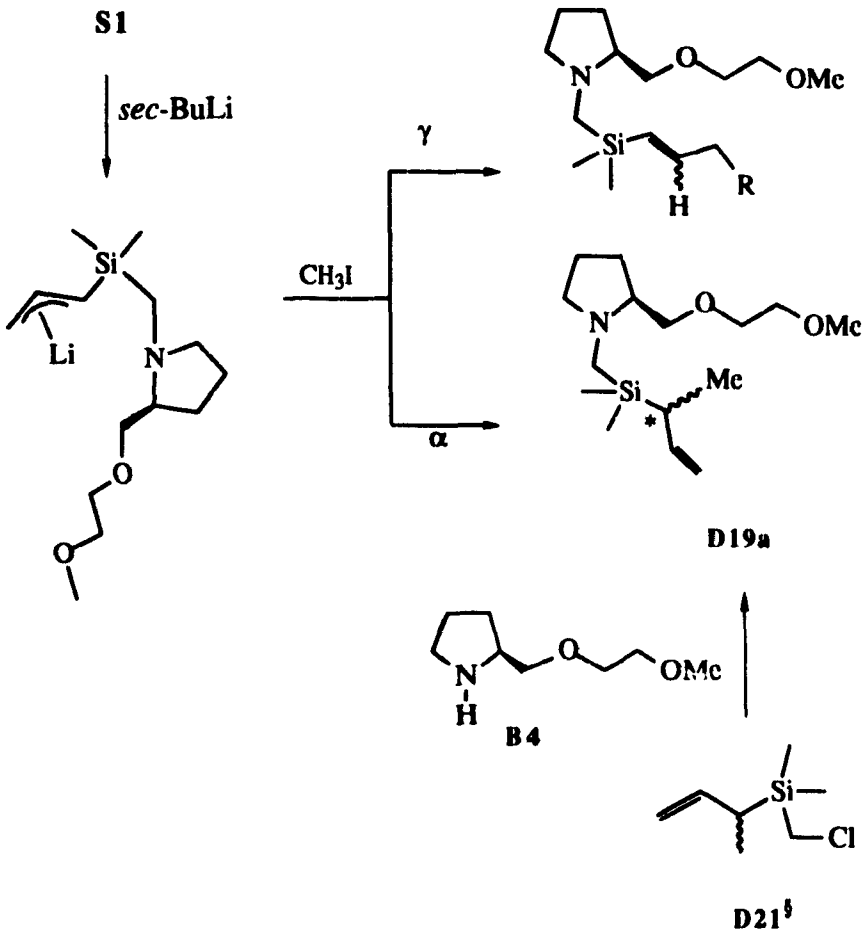
The α-stereoselection of the electrophilic alkylation of **S2** appeared to be excellent in all cases. The de of the methylated product **D19a** was determined by comparing with the NMR signal of the racemic mixture from the reaction of **D21** [20] with (S)-2-methoxyethoxymethylpyrrolidine (**B4**) (Scheme 4.9).

The ^{1}H-NMR signal of the characteristic ethylene protons of the pure diastereomer **D19a** from **S1** showed distinct simplicity cf. that from the racemic mixture (Fig. 4.1 and 4.2a,b). The characteristic methylene protons and the ^{13}C spectrum of the α-hexylated product **D20a** also displayed a single set of signal/multiplicity for a single diastereoisomer (Fig.4.3 and 4.4a,b).

These results, thus, showed that there was excellent stereochemical control from chelation between the chiral ligand and Li. Further more, the fact that for **D15** there was no solvent effect also suggested that at least a Li - O coordination bond existed, even in THF, for the regio- and stereochemical results. Therefore, it is believed that the first oxygen on the chelating chain (*vis.* **D15**) was important for binding with Li. Adding one more

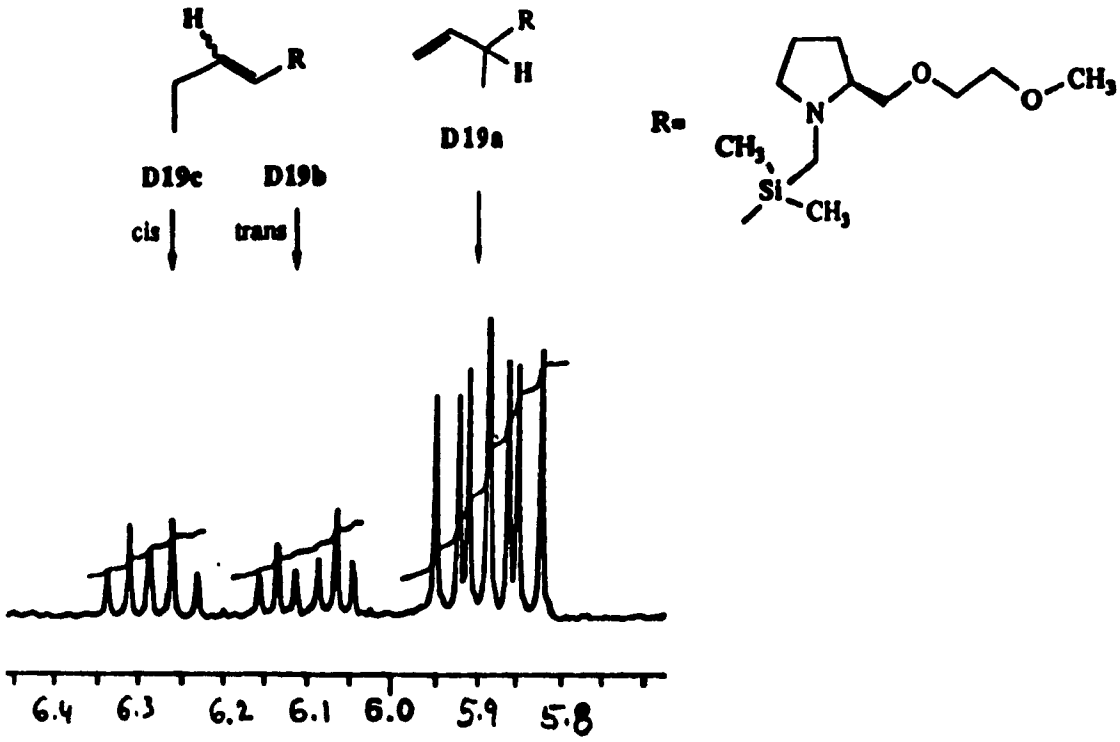
binding site (*vis.* **S1**) resulted in a tight chelate that should enhance α-selectivity. However, the ratio of the α– to γ–methylated product from **S1** was essentially the same as that from **D15**, which implied that the maximum α-selective had been reached with **D15** as the substrate, for the pyrrolidine silicon substituent series. Although solvent effect on stereoselectivity of the electrophilic alkylation reaction has been observed [13], it was not seen (or too small to be seen) in the cases of substrate **D15** and **S1**. This could mean that the reactivity of these substrates is so high that it overcame solvent effect.

Scheme 4.9 Synthesis of racemic D19a



§ : *chemical was inherited from R. Horvath*

Figure 4.1 ^{1}H NMR Spectrum of Olefinic Resonances of products D19a-c



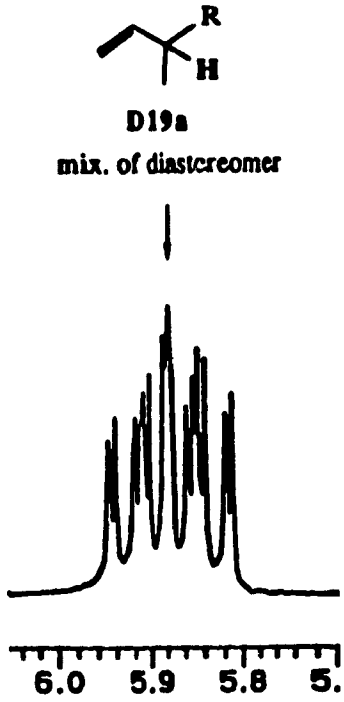


Figure 4.2a ^{1}H **NMR Spectrum of 1-{1-[2-(S)-(2-Methoxyethoxy)methyl]pyrrolidinyl}-2-sila-2,2,3-trimethyl-4-pentene (D19a)**

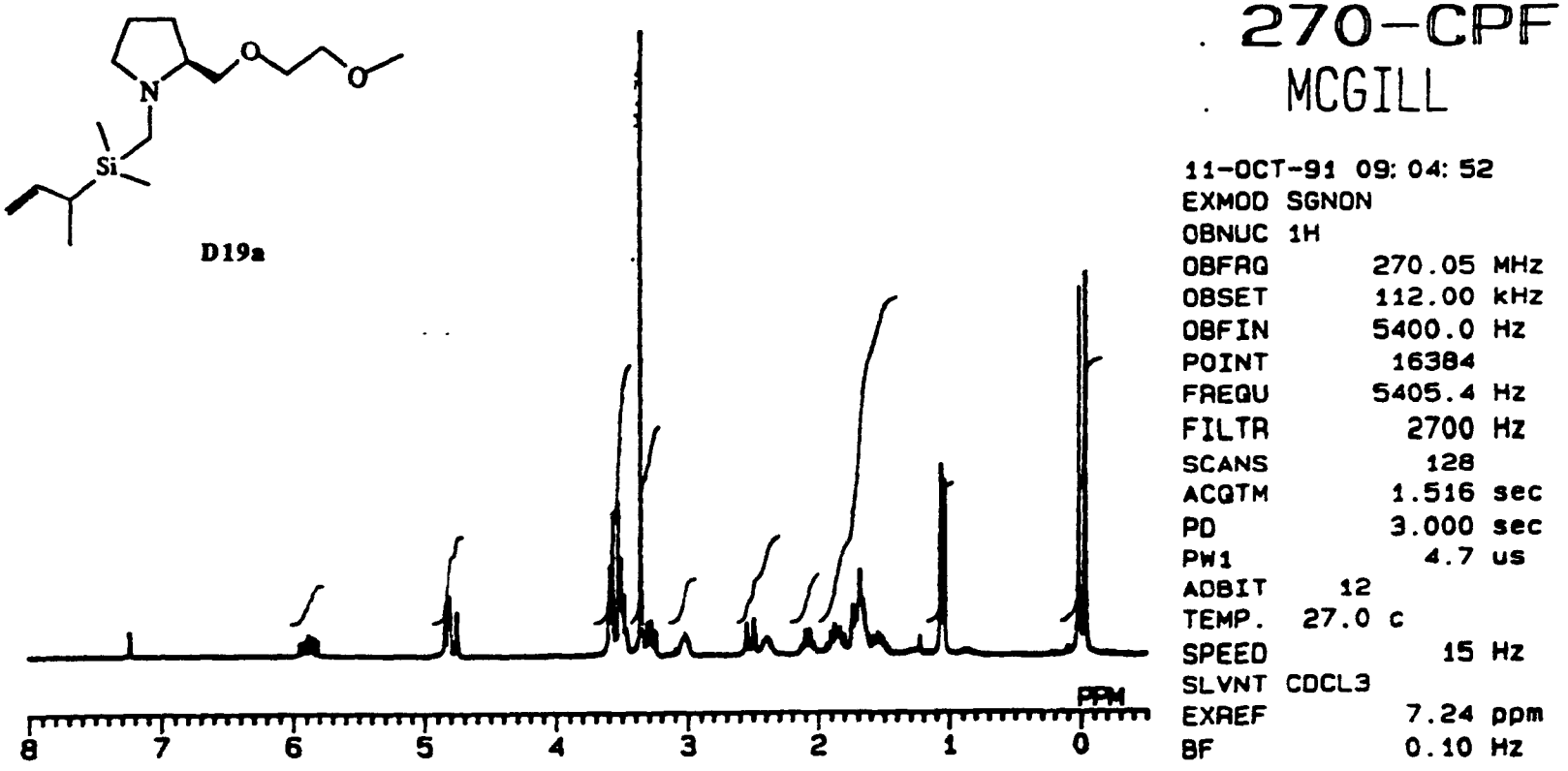
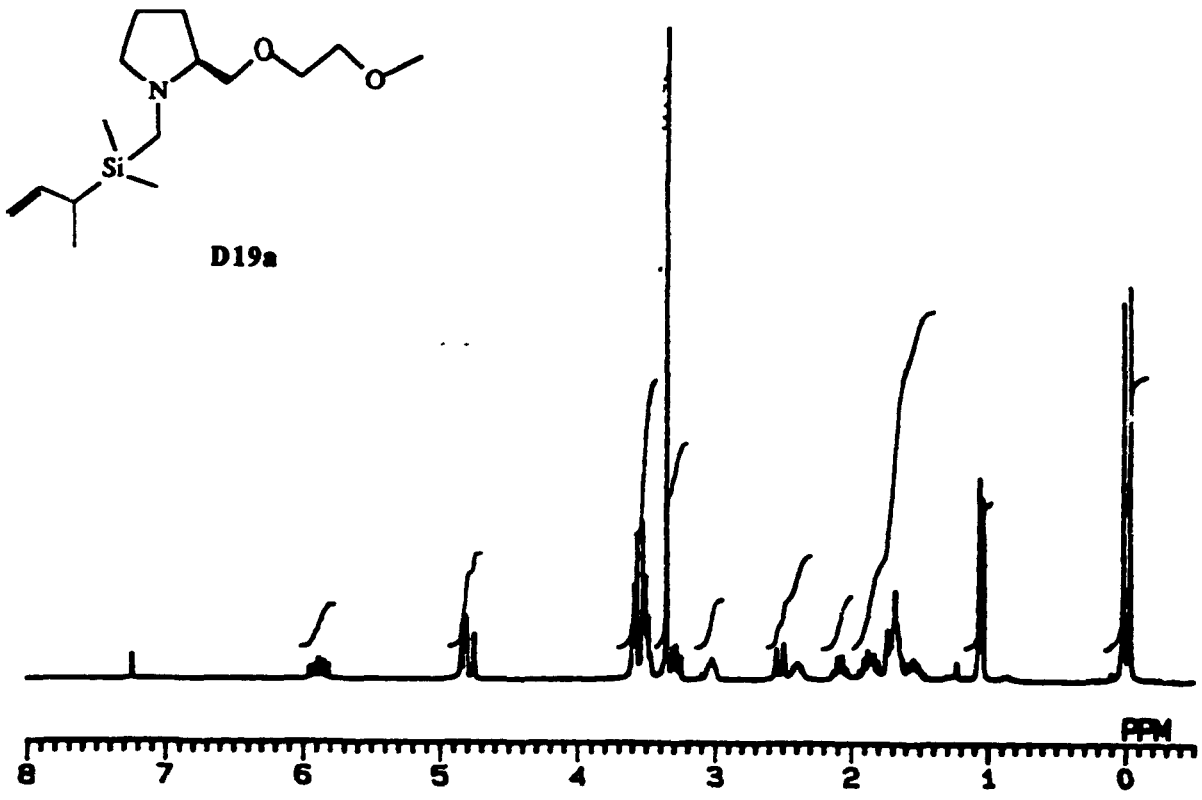


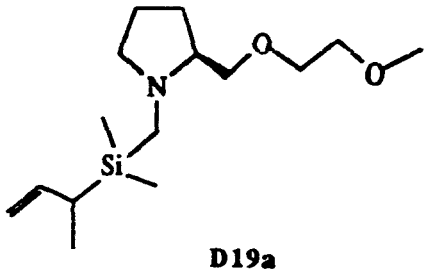
Figure 4.2a ^{1}H **NMR Spectrum of 1-{1-[2-(S)-(2-Methoxyethoxy)methyl]pyrrolidinyl}-2-sila-2,2,3-trimethyl-4-pentene (D19a)**



270-CPF
MCGILL

11-OCT-91 09: 04: 52
EXMOD SGNON
OBNUC 1H
OBFRQ 270.05 MHz
OBSET 112.00 kHz
OBFIN 5400.0 Hz
POINT 16384
FREQU 5405.4 Hz
FILTR 2700 Hz
SCANS 128
ACQTM 1.516 sec
PD 3.000 sec
PW1 4.7 us
ADBIT 12
TEMP. 27.0 c
SPEED 15 Hz
SLVNT CDCL3
EXREF 7.24 ppm
BF 0.10 Hz

Figure 4.2b ^{13}C **NMR Spectrum of 1-{1-[2-(S)-(2-Methoxyethoxy)methyl]pyrrolidinyl}-2-sila-2,2,3-trimethyl-4-pentene (D19a)**



D19a

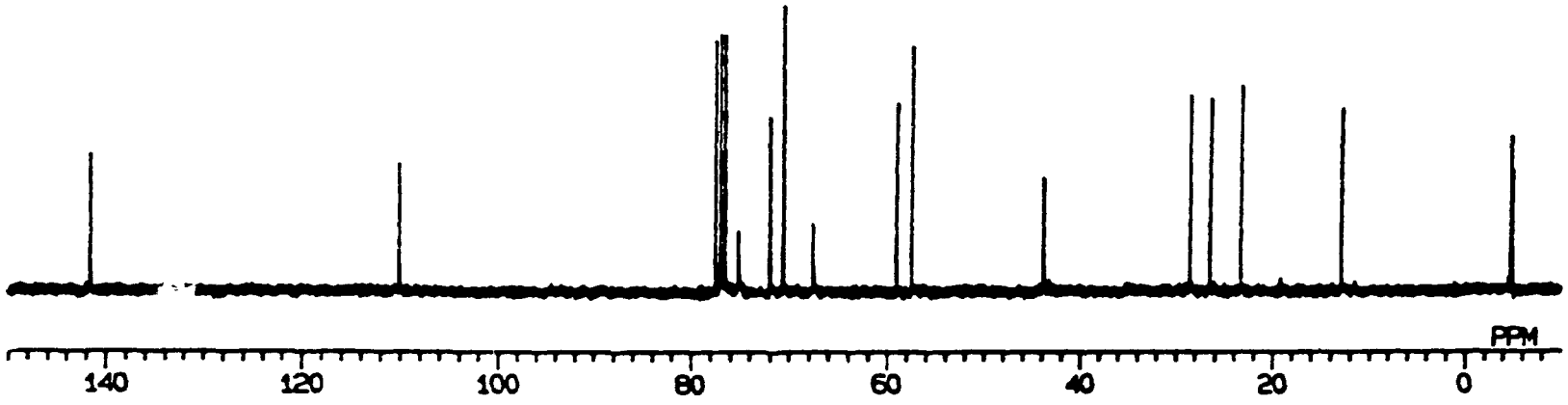


Figure 4.3 ^{1}H **NMR Spectrum of Olefinic Resonances of products D20a-c**

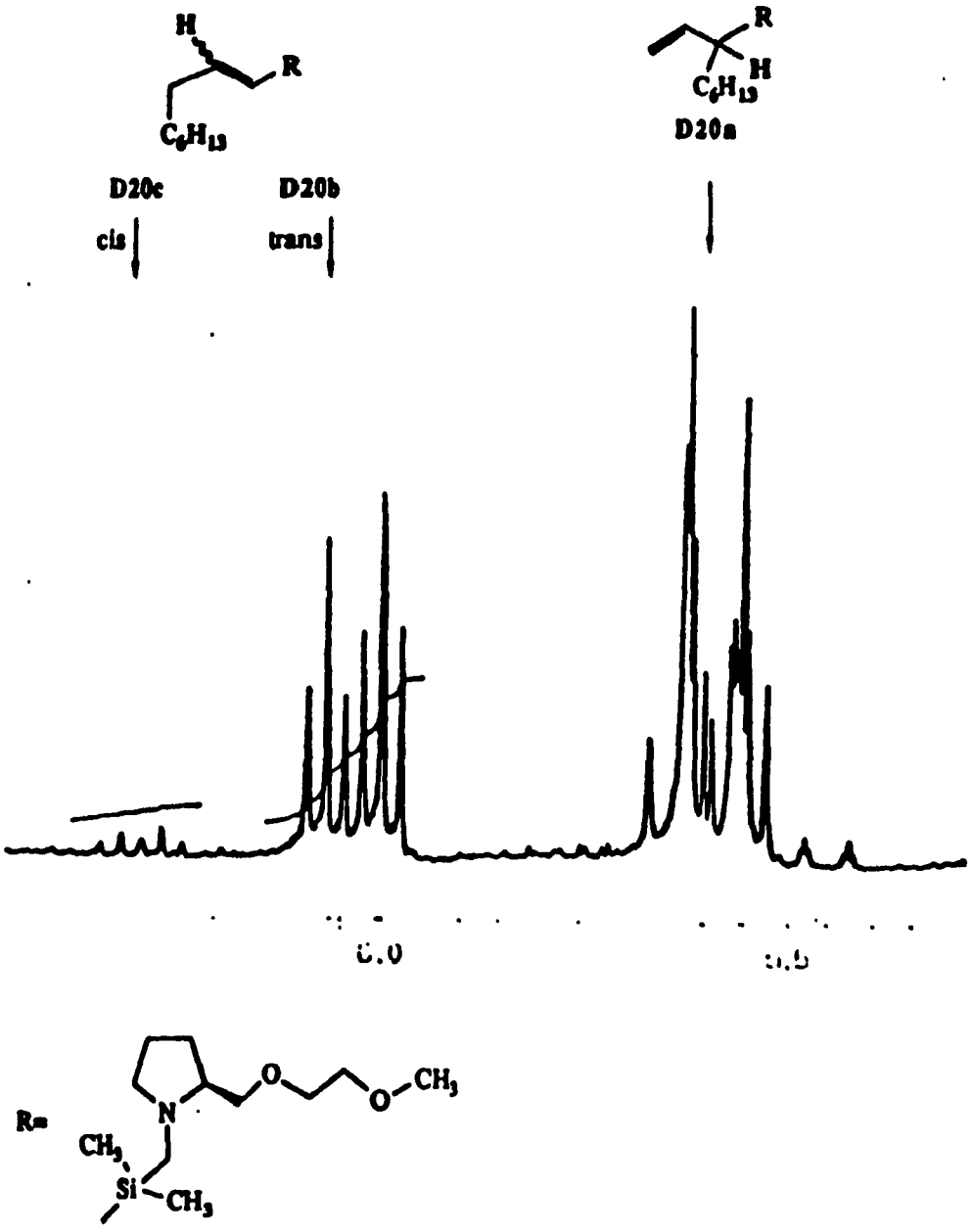
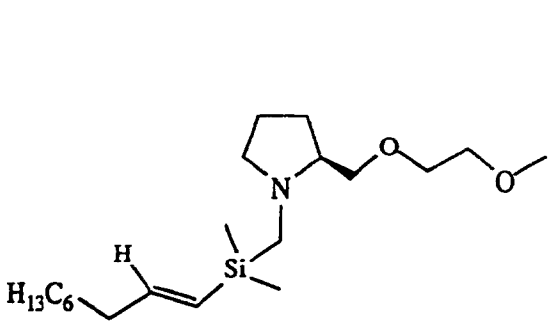
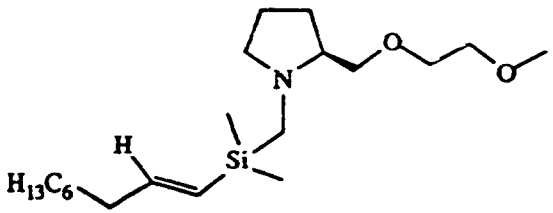


Figure 4.4a ^{1}H **NMR Spectrum of** *(E)*-2,2-dimethyl-1-{1-[2-(S)-(2-methoxyethoxy)methyl] pyrrolidinyl}-2-sila-3-undecene (D20b)

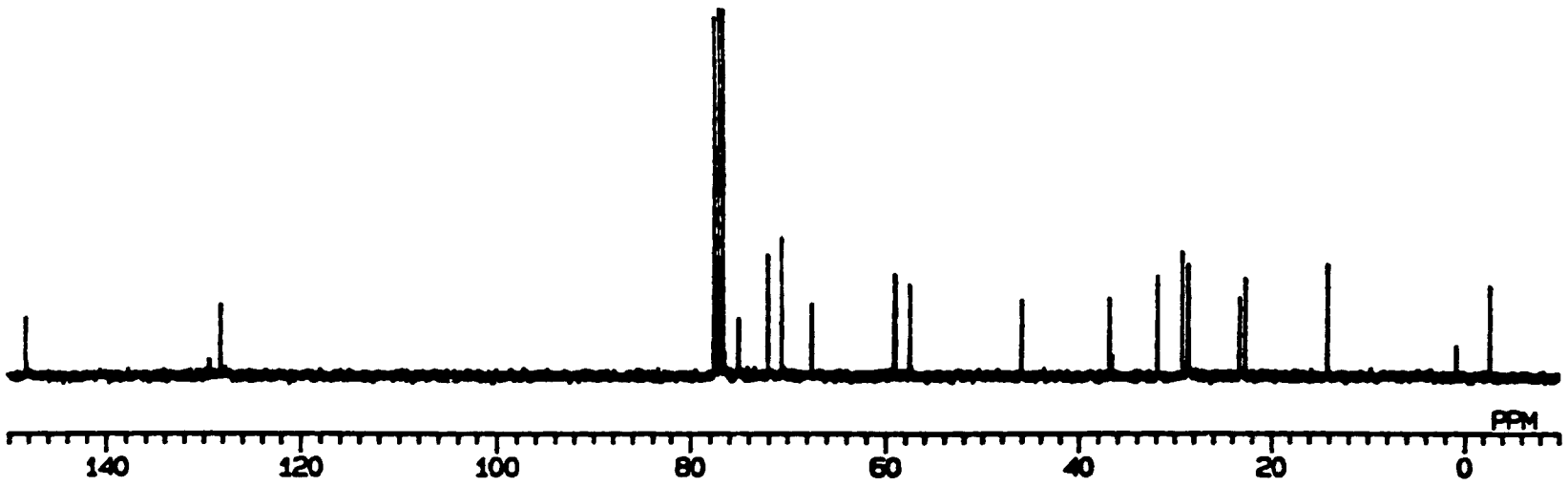


D20b

Figure 4.4b ^{13}C **NMR Spectrum of** *(E)*-2,2-dimethyl-1-{1-[2-(S)-(2-methoxyethoxy)methyl] pyrrolidinyl}-2-sila-3-undecene (D20b)



D20b



On hexylation, increasing the number of chelating site also increases the bulk on the allyl anion-Li complex. The intermediate chelated anion complex entities, **S1-d, e, f** (Scheme 4.6), should have the spatial structure as depicted in scheme 4.6 rather than the simplified structure as shown in scheme 4.7 and 4.8. Thus, increasing the bulk on the ligand would exert steric constrain on the nucleophilic attack of the allyl anion complex on the large HexI electrophile. Therefore, steric effect was more prominent with **S1** than **D15**. Methyl iodide was not big enough to have significant steric effect and differentiate between **S1** and **D15**.

III. CONCLUSIONS

Chelation between the chiral silicon substituent ligand and Li proved to be successful in the regio- and stereochemical control of the electrophilic alkylation of allysilanes. Thus, with no significant steric and solvent effect, α-selectivity is favored due to chelation as expected. Excellent stereoselectivity was also achieved by using chiral chelating ligand. These results also suggests a better regiocontrol, which promotes α-adduct, by carrying out the alkylation in a non-coordinating solvent with other better chiral chelating group.

The addition of another chelating site base on the pyrrolidine system proved to be unnecessary in improving the α-selectivity and stereocontrol of the reaction, however, large chelating ligand could be used to promote γ-alkylation.

EXPERIMENTAL SECTION

General Methods. Matterials were obtained from commercial suppliers unless noted otherwise. Reaction solvents were all freshly distilled. Distilled hexanes was used for column chromatography. Other solvents were reagent grade or better. Whenever is mentioned, water means distilled water. Analytical thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254}. Ninhydrin/ethanol or ceric acid mist was used for compound visualization. Flash chromatography analysis was done on Merck silica gel 60 (230 - 400 mesh ASTM). Capillary gas chromatography analysis was performed on a Hewlett Packard 5890A and 5890 Series II instruments fitted with a 25m x 0.2mm high performance column (cross-linked methylsilicon, film thickness of 0.33μm). Optical rotations were determined on the JASCO DIP-140 digital polarimeter. Infrared (IR) spectra were recorded on an Analect FT, AQS-18 spectrophotometer with a MAP-67 data system and are reported in reciprocal centimeters (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian, XL-200, XL-300 or JEOL-270 instruments. All NMR spectra were done with $CDCl_3$ as the solvent and internal standard. Chemical shifts are expressed in part per million (ppm). Significant ^{1}H NMR data are tabulated in the order: proton type, chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), coupling constant in Hertz (Hz) and number of protons. ^{13}C NMR data are expressed as type of carbon and chemical shift (ppm). Decoupling, DEPT, HETCOR, and COSY experiments were performed to unambiguously assign selected spectra. Low and high resolution mass spectra (MS) were obtained with Du Pont 21-492B and ZAB 2F HS mass spectrometer (EI, 70eV; CI, H^{+}) and are reported as m/e (relative intensity in percent).

General procedure for the electrophilic alkylation reactions [3]. 2,2-Dimethyl-1-{1-[(S)-2-(2-methoxy)ethoxymethyl]pyrrolidinyl}-2-sila-4-pentene (**S1**) (0.1055g, 0.4mmol) was dissolved in 2ml of solvent (ether or THF) at -78°C. *sec*-BuLi (0.6ml, 1.3M/hexanes, 0.8mmol) was then added and the solution stirred for 15 min. The alkylhalide (0.8mmol) was then added and the mixture stirred for another 15 min at -78°C. Brine was added and the reaction mixture gradually let warm up to room temperature. Extraction of the reaction mixture into ether, drying the organic phase over $MgSO_4$ and rotary evaporating of the solvent gave the crude product. Purification was done by flash chromatography with hexanes:ethyl acetate 10:1 as eluting solvent.

1-{1-[2-(S)-(2-Methoxyethoxy)methyl]pyrrolidinyl}-2-sila-2,2,3-trimethyl-4-pentene (D19a) and *(E)*- and *(Z)*-2,2-Dimethyl-1-{1-[2-(S)-(2-methoxyethoxy)methyl] pyrrolidinyl}-2-sila-3-hexene (D19b and D19c). ^1H NMR (270 MHz, $CDCl_3$) δ -0.08 and 0.03 (s, 6H), 1.05 (d, 3H, J=6.1 Hz), 1.08 (d, 1H, J=8.6 Hz, **D19a**), 1.48-1.95 (m, 4H), 1.80 (d, 1H, J=15 Hz), 2.09 (m, 1H), 2.4 (m, 1H), 2.51 (d, 1H, J=15 Hz), 3.03 (m, 1H), 3.37 (s, 3H), 3.28 (dd, 1H, J=10.8, 6.4 Hz), 3.45-3.62 (m, 5H), 4.73 - 4.86 (m, 2H), 5.1 (d, 1H,.J=18 Hz, **D19b**), 6.28 (d, 1H, J=12.9 Hz, **D19c**), 5.44 (dt, 2H, J=12.9, 7.3 Hz, **D19c**), 5.88 (m, 1H, **D19a**), 6.1 (dt, 1H, J=18, 6 Hz, **D19b**); ^{13}C NMR (67.8 MHz, $CDCl_3$) of **D19a** : δ -4.5, -4.3, 13.3, 23.8, 26.9, 29, 44.3, 58, 59.5, 68, 71.0, 72.4, 75.6, 142, 110.5; IR (neat) 530, 835, 1107, 1247, 1457, 1624, 2875, 2960 cm^{-1}; MS (EI) *m/z* 196 (100), 59 (34), 197 (21), 172 (20), 73 (12), 89 (9), 45 (9), 98 (9), 55 (7), 44 (7); **D19a** : $[\alpha]_D^{20}$ = -97° (c=0.336, $CHCl_3$).

2,2-Dimethyl-1-{1-[2-(S)-(2-methoxyethoxy)methyl]pyrrolidinyl}-2-sila-3-vinylnonane (D20a).and *(E)*- and *(Z)*-2,2-dimethyl-1-{1-[2-(S)-(2-methoxyethoxy)methyl] pyrrolidinyl}-2-sila-3-undecene (D20b and D20c). ^{1}H NMR (270 MHz, $CDCl_3$) δ -0.02 and -0.03 (s, 6H, **D20a**), 0.059 and 0.073 (s, 6H, **D20b**), 0.15 and 0.18 (s, 6H, **D20c**), 0.86 (t, 3H, J=6 Hz), 1.2 -1.4 (b, 10H), 1.48-1.95 (m, 4H), 1.73 (d, 1H, J=12.9 Hz), 2.06 (m, 2H), 2.08 (m, 1H), 2.09 (m, 2H, J=10.8 Hz, **D20a**), 2.39 (m, 1H), 2.48 (d, 1H, J=12.9 Hz), 3.03 (m, 1H), 3.29 (d, 1H, J=10.3, 7.0 Hz), 3.38 (s, 3H), 3.48-3.73 (m, 4H), 3.5 (m, 1H), 5.58 (d, 1H, J=16.9 Hz, **D20b**), 5.46 (d, 1H, J=13.5 Hz, **D20c**), 5.60 (m, 1H, J=10.8 Hz, **D20a**), 5.96 (dt, 1H, J=16.9, 6.1 Hz, **D20b**), 6.31 (dt, 1H, J=13.5, 7.5 Hz, **D20c**), 4.82 (m, 2H, **D20a**); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -2.71, -2.77, 14.09, 22.66, 23.21, 28.54, 28.66, 29.13, 31.82, 36.83, 39.16, 46.02, 57.51, 59.03, 67.43, 70.56, 71.97, 74.97, 128.13, 148.31.

Synthesis of racemic D19a from D21 and B4. The procedure was similar to that for the synthesis of S1. A neat mixture of S-2-[(2-Methoxyethoxy)methyl]pyrrolidine (**D4**) (0.27g, 1.7mmol) and 3-(chloromethyldimethyl)silyl-1-butene (**D21**) [20] (0.13g, 0.8mmol) was refluxed for 2hrs at 90-110°C in the presence of catalytic amount of NaI (20mg) and molecular sieves (3Å, 50mg). After cooling down to room temperature, brine was added and the reaction mixture extracted into ether. The organic phase was dried over $MgSO_4$ and rotary evaporating of the solvent gave the crude product. Purification by flash chromatography with hexanes:ethyl acetate 4:1 as eluting solvent.gave 1.98g of the crude product. Purifying by flash chromatography (hexanes:ethyl acetate 4:1) gave 0.15g (80%) of the pure racemic product **D19a**. ^{1}H NMR : similar to **D19a** above, with added signals from the diastereomeric a-allyl proton at 5.88ppm, as shown in figure 4.1.

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