PROCESSING OF THE DIBAL ADDUCT OF A PROLINE-DERIVED ESTER TO GENERATE A SINGLE DIASTEREOMER OF AN ALLYL ALCOHOL FOR USE IN A NOVEL SYNTHETIC METHOD FOR PYRROLIZIDINES

by

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Using the method of intramolecular carbolithiation in which the organolithium is generated by reductive lithiation of a phenyl thioether, annulations on to pyrrolidine derivatives have been accomplished to produce virtually enantiomerically and diastereomerically pure pyrrolizidines. However, the main part of the thesis involves mechanistic and theoretical studies of the highly diastereoselective process by which a key intermediate, (*S*,*S*)-2-pyrrolidinyl vinyl carbinol **6** used, in the synthesis of a hydroxylated pyrrolizidine, is generated from *N*-Boc-*L*-proline methyl ester.

The process involves the treatment of this ester with DIBAL at -78 °C, warming to -20 °C, cooling to -78 °C, and treatment with vinylmagnesium bromide. It was demonstrated that there is virtually no stereoselectivity when the vinylmagnesium bromide is added to the corresponding aldehyde in the presence of di-isobutylaluminum methoxide, the products expected if the DIBAL-ester adduct decomposes before Grignard addition. Further evidence that an aldehyde is not involved was obtained when it could not be detected by ^{1}H NMR in the solution after warm-up.

The theoretical study was designed to test a postulated mechanism in which a mixture of diastereomeric adducts **R1** and **R2** of DIBAL and the ester, generated at -78 °C, undergoes equilibration by reversible ionization of the methoxide ion when warmed and that the isomer **R1**

greatly predominates at equilibrium. Both diastereomers are believed to involve a seven-membered ring, afforded by coordination of the Al atom of the adduct with the carbonyl oxygen atom of the Boc group, fused to the pyrrolidine. Reaction of the diastereomer **R1** with vinylmagnesium bromide via a S_Ni mechanism would yield the observed diastereomer of the allylic alcohol.

Calculations do indeed predict that **R1** is substantially more stable than its diastereomer **R2** providing evidence for the mechanism. As a bonus, it has been discovered that the same high stereoselectivity can be attained without raising the temperature by adding a catalytic amount of the Lewis acid $ZnCl_2$ at -78 °C; the Lewis acid probably aids the ionization of the methoxide ion thus increasing the rate of equilibration, providing an additional piece of evidence for the mechanism as well as simplifying the experimental procedure.

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PREFACE

I wish to express sincere gratitude to my advisor Dr. Cohen for his guidance, inspiration, and encouragement throughout my graduate program. This work could not have been done without Dr. Cohen expert advice and strong support. I also wish to warmly thank Dr. Cohen for his understanding and help on my personal issues.

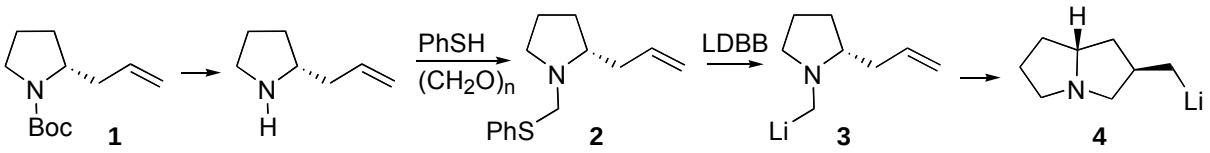
My sincere appreciation extends to my graduate committee members: Dr. Chapman and Dr. Nelson for critical review of my thesis and their invaluable assistance. I am grateful to Dr. Jordan for his help during the computation calculation.

My special thanks also go to my labmates, my friends and family who have supported me throughout my research.

Finally, this work is in memorial of Xueying Shan, my always beloved mom, who passed away last year in her early fifties. My mom is always the support of my life.

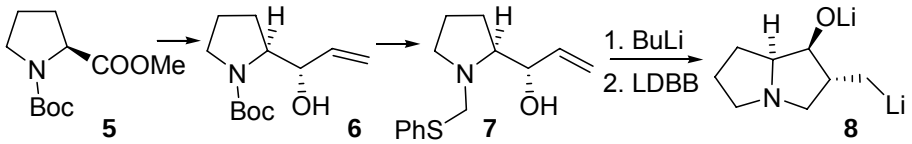
1. INTRODUCTION

The original goal of this research was the development of a new method of preparation of pyrrolizidines utilizing cyclization by intramolecular carbolithiation whereby the organolithium is prepared by reductive lithiation of phenyl thioethers by aromatic radical-anions.[1] For example in Scheme 1.1, the known compound **1** could be deprotected and converted to **2** which, upon reductive lithiation with the aromatic radical-anion lithium 4,4'-di-*tert*-butylbiphenylide (LDBB), would yield the organolithium **3** that would be expected to cyclize to **4**; the background for such a reaction scheme is given in Chapter 3.



Scheme 1.1 Synthetic route of compound **4**

The more functionalized pyrrolizidine **8** could arise from similar processing of the known allyl alcohol **6**, generated from the protected proline ester **5** by treatment with diisobutylaluminum hydride (DIBAL) at -78 °C, warming the adduct to -20 °C and adding vinylmagnesium bromide (see Scheme 1.2).[2] A study of this type of stereoselective conversion of **5** to **6** is discussed in Chapter 2 while the cyclization of **7** is discussed in Chapter 3.



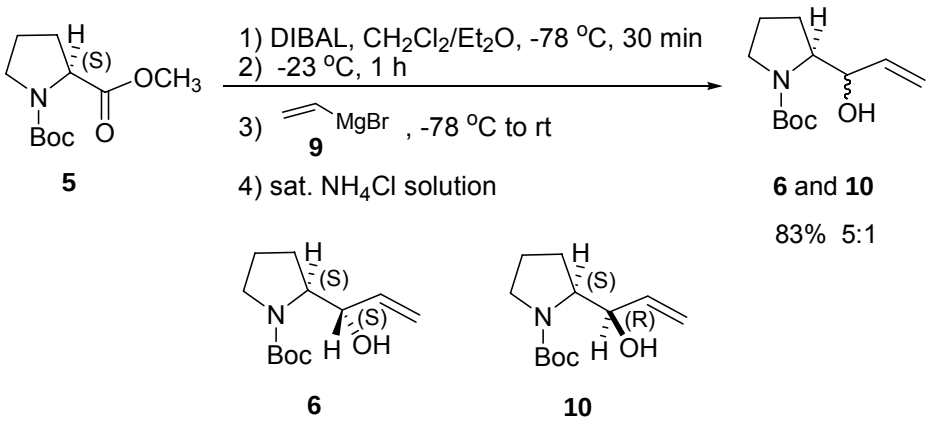
Scheme 1.2 Synthetic route for compound **8**

2. PROCESSING OF THE DIBAL ADDUCT OF A PROLINE-DERIVED ESTER TO GENERATE A SINGLE DIASTEREOMER OF AN ALLYL ALCOHOL

2.1. Introduction

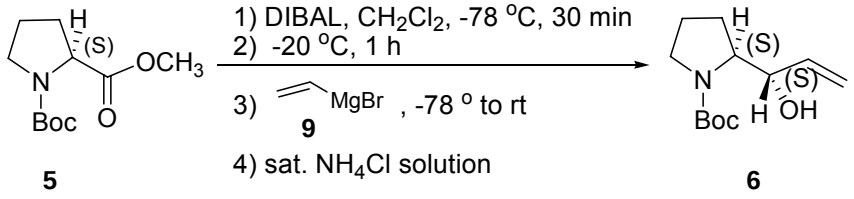
2.1.1. Previous work on the addition of Grignard reagents to DIBAL adducts of α-aminoester derivatives to generate β-amino secondary alcohols diastereoselectively

As mentioned in Chapter 1, we required vinyl 2-pyrrolidinyl alcohol **6** for our projected synthesis of pyrrolizidines. Taguchi[2] has reported the addition of vinylmagnesium bromide **9** to the DIBAL adduct of *N*-Boc-*L*-proline methyl ester with some diastereoselectivity. In his experiment, **5** was treated with DIBAL at -78 ^{o}C followed by a warm-up step to -23 ^{o}C before addition of the Grignard reagent at -78 ^{o}C as shown in Scheme 2.1. He obtained the β-amino secondary alcohol **6** (see Scheme 2.1) and its diastereomer in 83% yield and 5:1 diastereomer ratio as determined by the MTPA method. According to this method, the diastereomers were converted into the *S*- and *R*- 2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) esters, which had different chemical shifts.[2]



Scheme 2.1 Taguchi's reduction/alkylation of *N*-Boc-*L*-proline methyl ester **5**

In our study, a similar reaction as shown in Scheme 2.2 was performed with a change in solvent and a minor change in temperature of the warm-up. We obtained one diastereomeric protected β-amino secondary alcohol **6** in 62% yield. The stereochemical assignment for secondary alcohol **6** is based on the NMR data of the two known diastereomers.[3] The purified diastereomer ratio of **6** to **10** was found to be greater than 32 to 1 by NMR analysis of the crude product. This ratio is also consistent with the gas chromatographic (GC) analysis (see Experimental section) .

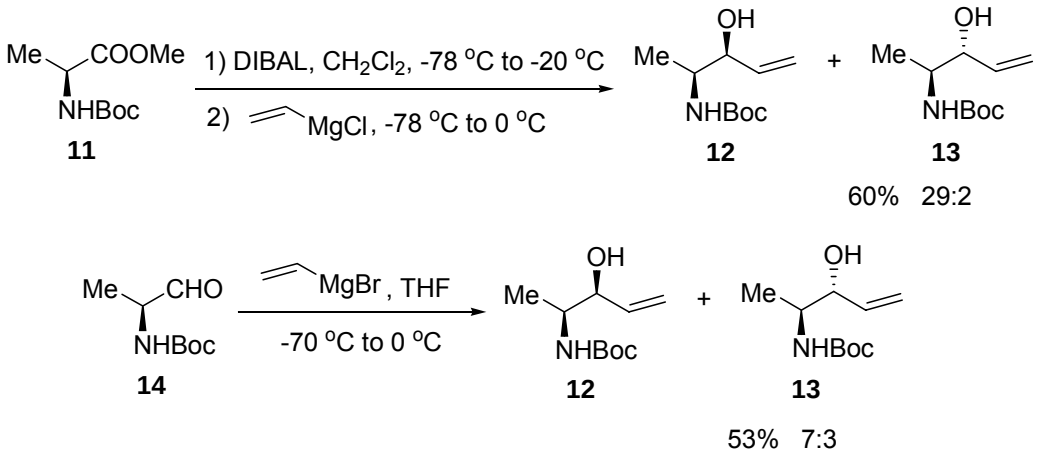


Scheme 2.2 Modified reduction/alkylation of *N*-Boc-*L*-proline methyl ester **5**

This high diastereoselectivity was very attractive. A literature search revealed that Taguchi was not the first to use the addition of an organometallic to the DIBAL adduct of an amino ester derivative to generate a β-amino secondary alcohol. The earliest work on this method was reported by Ibuka, Fujii, Yamamoto and co-workers.[4]

These authors observed a dramatically increased diastereoselectivity (29:2), as comparing to that 7:3 obtained from the reaction of the Grignard reagent to the corresponding aldehyde as starting material when *t*-Boc-protected methyl alaninate was treated sequentially with DIBAL and vinylmagnesium chloride (Scheme 2.3). In their report, it is notable that they creatively added a warm-up step from -78 ^{o}C to -20 ^{o}C before Grignard reagent treatment at -78 ^{o}C. This makes their method different from the previously used DIBAL reduction methods of derivatives of esters of α-amino acids when addition of DIBAL is directly followed by addition of the Grignard reagent without any warm-up.[5] To simplify the later discussions, we call the method with a warm-up step after the addition of DIABL and before the addition of Grignard reagent "the advanced ester reduction/alkylation".

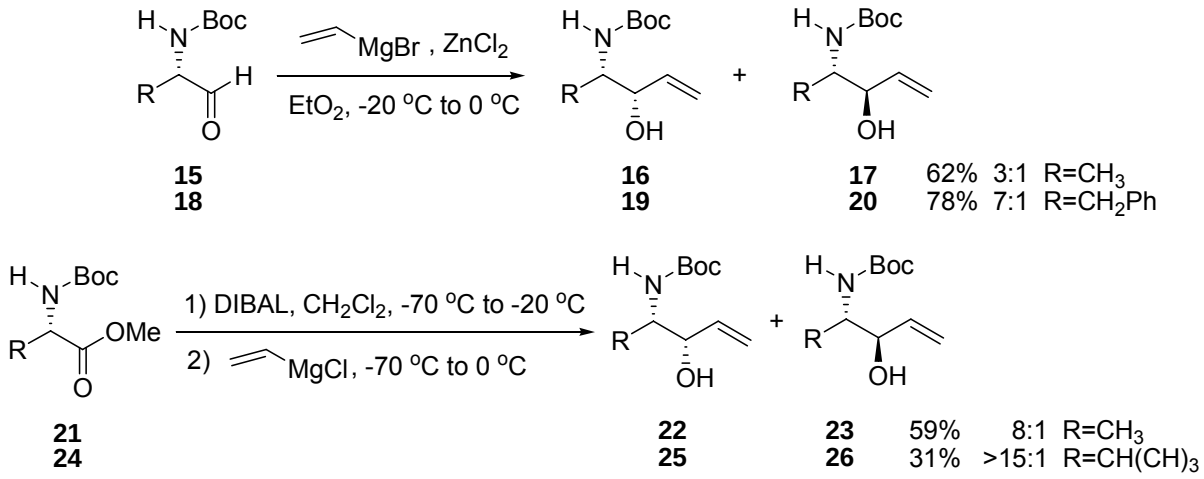
In their experiment (Scheme 2.3), *N*-Boc-(*S*)-methylalaninate **11** was first reduced by DIBAL at -78 ^{o}C and the reaction mixture was then warmed to -20 ^{o}C for 30 min. It was then re-cooled to -78 ^{o}C before the addition of vinylmagnesium chloride. This experimental procedure gave excellent diastereoselectivity. The diastereomer ratio was 29:2 for syn **12** and anti **13** allyl alcohols in 60% combined yield. This ratio is superior to that obtained from the reaction of Boc-(*S*)-alaninal **14** with vinylmagnesium bromide (THF, -70 ^{o}C to 0 ^{o}C). The latter gave a mixture (7:3) of syn and anti allyl alcohols in 53% combined yield.



Scheme 2.3 Advanced ester reduction/alkylation of Boc-(*S*)- methylalaninate **11** and addition of vinylmagnesium bromide to Boc-(*S*)-alaninal **14** by Ibuka, Fujii and Yamamoto[4]

Angle later also achieved high diastereoselectivity when he applied the advanced ester reduction/alkylation in the synthesis of β-amino secondary alcohols after he did not obtain ideal selectivity using aldehydes as starting material.[6] Illustrated in the upper panel of Scheme 2.4 are two reactions starting from the aldehydes **15** and **18**. The desired amino alcohols **16** and **19** are the products of a chelation-controlled (cyclic Cram) addition to the aldehyde. The mechanism of the chelated transition state will be discussed in detail in section 2.1.2 (see (c) in Figure 2.1, R=CH_3). This reaction gave allyl alcohols in 62% yield as a 3:l mixture of syn/anti diastereomers **16** and **17** when R=CH_3 and in 78% yield as a 7:l mixture of syn/anti diastereomers **19** and **20** when R=CH_2Ph. However, when the advanced ester reduction/alkylation is used, they observed an enhancement in the stereoselectivity during the transformation of *N*-Boc-alanine methyl ester to amino alcohol in a one pot reaction upon the sequential addition of DIBAL and vinylmagnesium chloride. The advanced ester reduction/alkylation afforded allyl alcohol products in 59% yield as an 8:1 mixture of diastereomers **22** and **23** when R=CH_3 and in 31% yield of alcohol **25** as a single diastereomer

when R=$CH(CH)_3$. The excellent selectivity makes this one-pot procedure the method of choice for selectively preparing amino alcohols.



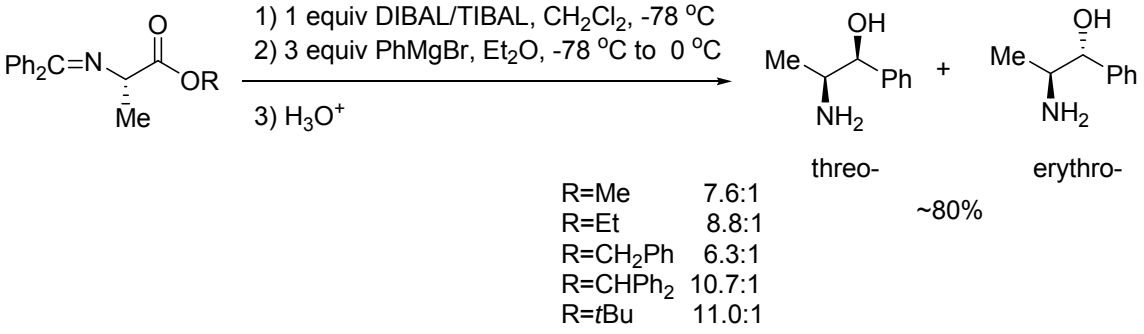
Scheme 2.4 Addition of vinylmagnesium chloride to *N*-Boc protected aminoaldehyde (**15** and **18**) and advanced ester reduction/alkylation of *N*-Boc protected amino acid methyl esters (**21** and **24**) by Angle

In summary, there are several ways starting from α-amino acid derivatives to make α-amino secondary alcohols diastereoselectively.

i) In one of the methods, where an α-amino acid is utilized as a source of chirality, a suitably protected amino acid ester is first converted to its corresponding aldehyde. The optically active protected aminoaldehyde then reacts with various carbon nucleophiles. This method is straightforward and is of potential synthetic value.[4,7-25] However, it usually suffers from configurational instability (enolization) under a range of reaction conditions, and the stereoselectivities in these reactions are often not ideal.[5,26-34]

ii) By virtue of the stability of α-aminoesters to epimerization, *D*-esters are better starting materials for syntheses of β-amino secondary alcohols than aldehyde. The method of DIBAL reduction followed by alkylation of the α-aminoesters to β-amino secondary alcohols is

straightforward. The DIBAL reduction/alkylation method by treating some chiral protected α-amino esters with DIBAL and Grignard reagent sequentially without the warm-up step can give good selectivity under some circumstances.[35-39] As illustrated in Scheme 2.5, Polt[40] observed a high threo- α-amino secondary alcohol yield (73-85%) and excellent "syn" stereoselectivity (8:1 to 11:1, threo or like product preferred) in the experiment when he treated optically pure imine-protected amino esters with DIBAL or DIBAL/TIBAL(*i*-Bu_3Al), followed by RMgX or RLi.



Scheme 2.5 DIBAL-reduction/alkylation of Schiff base esters to phenylpropanolamines

iii) The advanced ester reduction/alkylation involves a sequential treatment of *N*-Boc-α-amino esters with DIBAL and, after a warm-up step, Grignard reagents, as demonstrated in Schemes 2.1 and 2.2 mentioned above. The advanced ester reduction/alkylation method gives higher selectivity than that from treating the aldehyde with a Grignard reagent or not employing the warm-up period.

2.1.2. Mechanism study of DIBAL reduction followed by addition of organometallic to generate β-amino secondary alcohols diastereoselectively

In brief, there have been mainly three methods to synthesize α-amino secondary alcohols diastereoselectively from α-amino acid derivatives. The first method of reacting the

aminoaldehyde with carbon nucleophiles has been extensively studied and its mechanism has been well established. The mechanism of the second method, the sequential addition of hydride and C-nucleophile has been studied without much success. The third method, as described above, which is the advanced ester reduction/alkylation method to synthesize β-amino secondary alcohols from α-amino esters greatly increases the stereoselectivity. Thus, it is an ideal method to synthesize optically pure amino alcohols. However, to date, no mechanistic explanation has been provided for this high stereoselectivity. Thus, in the following section of this Chapter, the reported mechanistic studies for the first two methods will be summarized.

Many researchers had made efforts to elucidate the mechanism(s) leading to diastereoselectivity in the method of synthesizing β-amino secondary alcohols from α-aminoaldehydes through addition of organometallic reagents. As Duhamel demonstrated in his work with racemic *N*,*N*-dialkyl-α-amino aldehydes, a Felkin-Ahn-type transition state, as shown in Figure 2.1 (a), can explain the erythro products[41,42] that are formed; it is believed that there is steric interference by the bulky benzyl groups with the chelating-ability of the nitrogen lone pair. When smaller groups are attached to nitrogen (e.g. *N*,*N*-dimethyl substitution), chelation is allowed.[43] However, removal of the protection from nitrogen poses a problem here when using groups such as methyl. Fortunately, with the efforts of many researchers in this field, several solutions have been provided for this problem. Reetz "tied back" the benzyl groups to favor the chelated transition state as shown in Figure 2.1 (b). In this transition state, the benzylic protection could be easily removed in the downstream reactions.[21] It has been reported by several other groups[4,13,15] that acyl-protected amines can provide an anionic chelated transition state as shown in Figure 2.1 (c), when the N-H proton is removed to generate an anionic nitrogen.

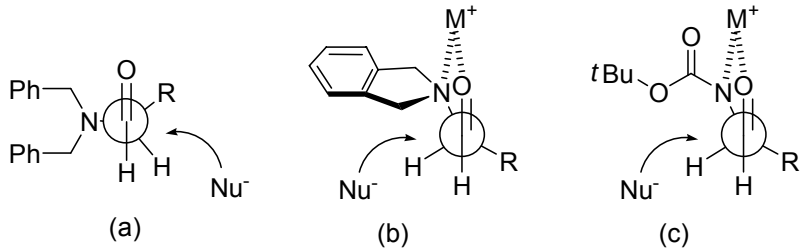
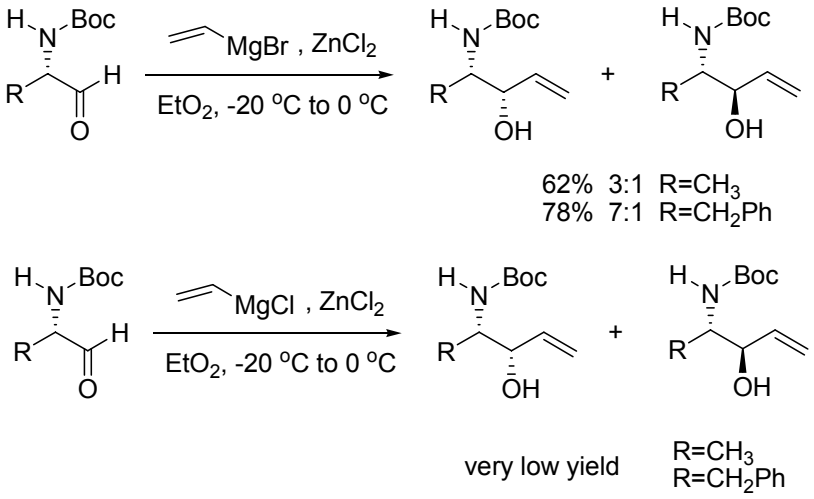


Figure 2.1 Several proposed transition states for stereoselective additions to protected amino aldehydes

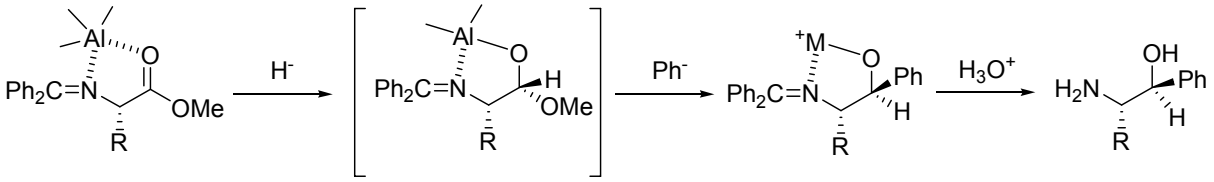
As demonstrated in Scheme 2.6, a minor modification in the reaction conditions can dramatically change the course of this reaction. With a small reaction condition change (e.g. H_2C=CHMgC1 vs H_2C=CHMgBr), deprotonation can generate a chelating substrate from a substrate which normally undergoes Felkin-Ahn addition.[41-43] Thus, the relative rate of deprotonation vs addition becomes extremely important in these reactions. With the chelated transition state mechanism described previously, this phenomenon becomes readily understandable. H_2C=CHMgBr can deprotonate the nitrogen atom more efficiently than H_2C=CHMgC1 and form a better chelated transition state.



Scheme 2.6 Addition of different Grignard reagents to aldehydes

Scheme 2.7 and Figure 2.2 are directly adapted from Polt's paper. The discussion is also based on his paper in which his explanation didn't fit his experimental data. We also have many questions concerning on his explanation.

To date, there is no universally accepted mechanistic interpretation for the results of the sequential addition of hydride and C-nucleophiles to the protected α-amino ester. Some researchers believe that the observed threo selectivity is due to an aluminum-chelated *N*-*t*-Boc-amino aldehyde (Cram cyclic transition state) as the intermediate. As shown in Scheme 2.7, Polt attempted to interpret the stereoselectivity for his reactions in Scheme 2.5 by invoking the cyclic Cram chelate model, with tri-*sec*-butylaluminum behaving as a chelation agent, for initial hydride delivery to the ester, followed by subsequent inversion of configuration in the displacement of the methoxide ion by the incoming nucleophile.



Scheme 2.7 Cram chelate model for initial hydride delivery to the ester

In his report, Polt postulated that Schiff base esters permit the chelation controlled addition of hydride (transition state (a) in Figure 2.2) at low temperature. He believes that a portion of the desired threo products arises from transition state (b) after the methoxide ion has been lost (S_N1-like pathway), although some products may arise from transition state (c) (S_N2-like pathway after delivery of the hydride ion). Currently, it is not possible to either confirm or deny the possibility that the aluminoxy acetals can exist as tight ion-pairs (d) or (e) (Figure 2.2) based on the available data. The conversion from an S_N2-like to an S_N1-like mechanism may not account for the decrease in diastereoselectivity observed with coordinating solvents. This decrease may be

due to increased "leakage" between the two structures (d) and (e). If there was an equilibration between the two ion-pairs, eclipsing interactions between the R group and the R'O group should favor of structure (e). As presented in Scheme 2.5, this may not be the case; that is to say, configurational equilibration (inversion) of the aluminoxy acetal via ion-pair rearrangement may not be a major pathway, at least under the condition of low temperature and absence of THF. The parallel increase in stereoselectivity with steric bulk of the ester in Scheme 2.5 is in the opposite direction to what one would expect from the ion-pair rearrangement. With the ion-pair rearrangement, one would expect decreased selectivity because the equilibrium (d) ⇌ (e) should shift to the right as the steric bulk of the R'O group increases.

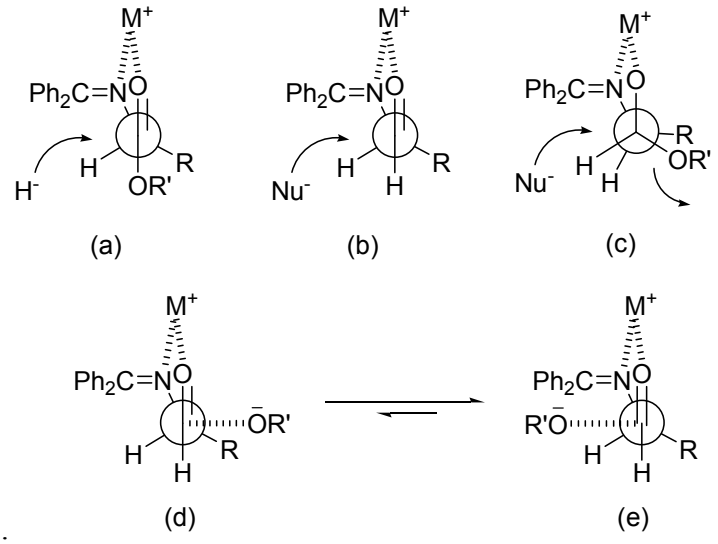


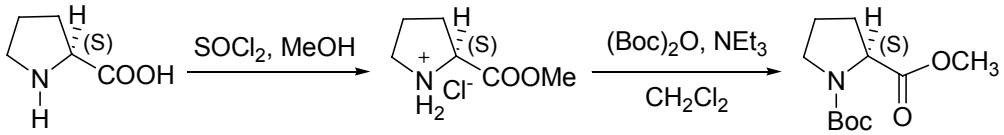
Figure 2.2 Mechanistic hypotheses by Polt

2.2. Results and Discussion

2.2.1. Wide application of advanced ester DIBAL reduction/alkylation with organometallics

As mentioned above, the advanced ester reduction/alkylation method, with a warm-up step, provides the significant advantage of high stereoselectivity, for the DIBAL reduction and subsequent Grignard reaction using protected α-amino esters as starting material. To date, there has been no systematic study on this method and its mechanism has not been elucidated. Thus, further study on this advanced ester reduction/alkylation method, with a warm-up step, is a worthwhile project in the development of procedures to make optically pure amino acids with high diastereoselectivity.

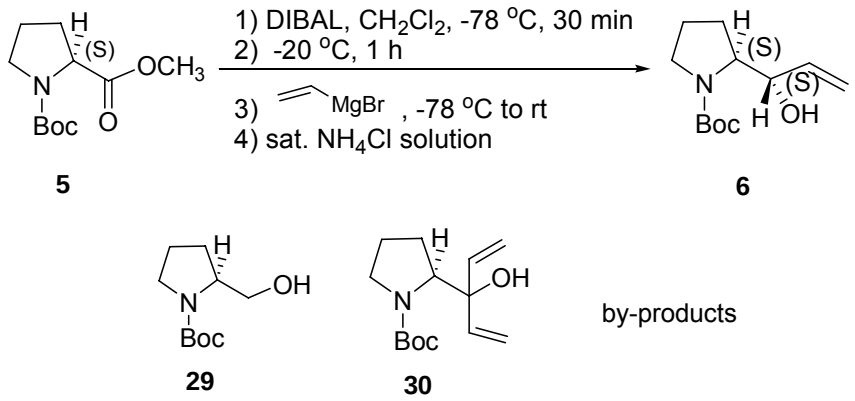
The requisite *N*-Boc-*L*-proline methyl ester **5** was readily prepared in good yield by known methods from *L*-proline **27** (Scheme 2.8). Briefly, *L*-proline **27** was first esterified with methanol via the acid chloride to give the corresponding methyl ester as the hydrochloride. The salt of the methyl ester **28** was then neutralized, followed by the treatment of the resulting amine with di-*tert*-butyl dicarbonate. This method afforded *N*-Boc-*L*-proline methyl ester **5** in 85% yield over two steps after purification by flash chromatography.[44] The optical rotation of the product **5** agreed with the reported values for optically pure *N*-Boc-*L*-proline methyl ester **5**.[45-47] The optical purity establishes that there was no racemization during this synthesis.



27 **28** **5** 85%

Scheme 2.8 Synthesis of *N*-Boc-*L*-proline methyl ester **5**

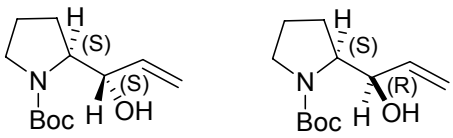
N-Boc-*L*-proline methyl ester **5** was used as the substrate for the advanced DIBAL ester reduction. It is very interesting and exciting that only a single distereomer was observed. As shown in Scheme 2.9, *N*-Boc-*L*-proline methyl ester **5** was first reduced by DIBAL at -78 ^{o}C and the reaction mixture was then warmed to -20 ^{o}C for 1 h. The reaction mixture was then re-cooled to -78 ^{o}C before the addition of vinylmagnesium bromide. This experimental procedure gave secondary alcohol **6** in approximately 80% yield. The by-products mainly include i) the over-reduced primary alcohol **29**, which is the common side-product of DIBAL reduction of esters, and ii) the tertiary alcohol **30** which is generated from reaction of one molecule of the ester **5** and two molecules of the Grignard reagent.



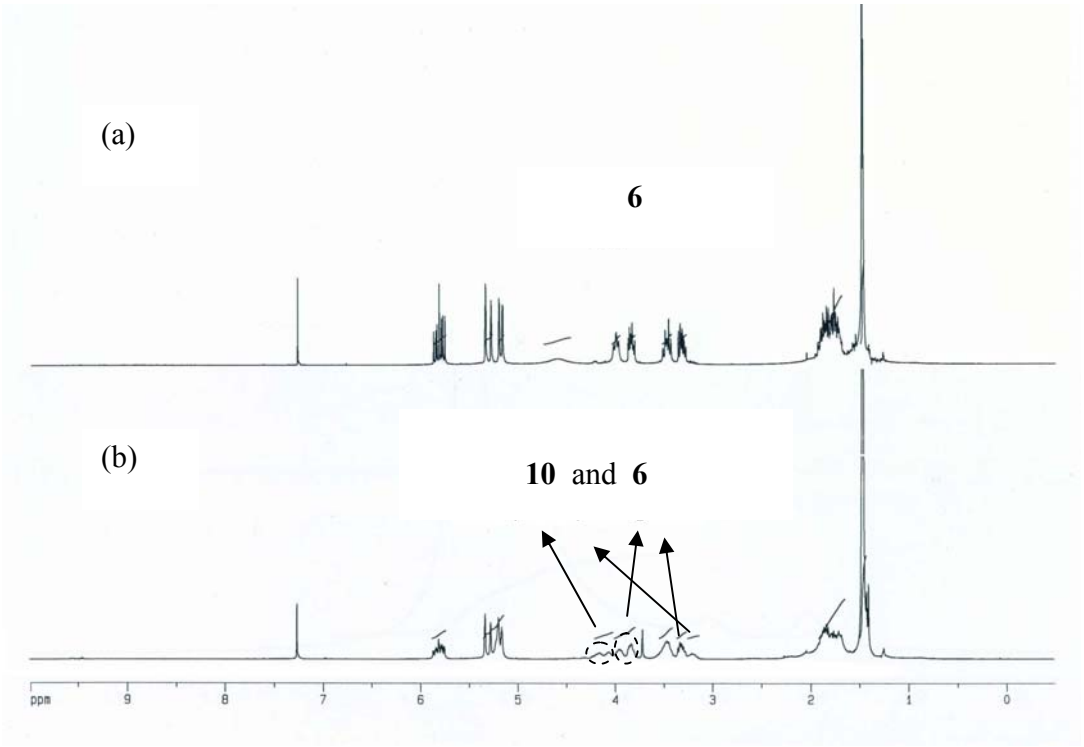
Scheme 2.9 Advanced ester reduction/alkylation of *N*-Boc-*L*-proline methyl ester **5** by vinylmagnesium bromide

The stereochemical assignment for secondary alcohol **6** is based on the NMR data of the two known diastereomers.[3] In fact, it is simple to determine the stereochemistry of the reaction products by comparison of their NMR spectra. As shown in Figure 2.3, (a) is the NMR spectrum of the product from the reaction in Scheme 2.9，and (b) represents the NMR spectrum of a mixture of two diastereomers **6** and **10** which are produced from other reactions that will be discussed in the later chapter. In (b), there are four peaks at around 4 ppm. Based on the known

NMR data of diastereomers **6** and **10**, we can assign the left two peaks, at lower field than 4 ppm, to **10**, and the right two peaks, at higher field than 4 ppm, to **6**. Another area in the spectrum that we can use to distinguish **6** and **10** is that between 3.0-3.5 ppm. In this range of the spectrum, the two marked peaks belong to **6** and **10,** respectively. It is obvious from comparison of the expanded spectra (c) and (d) in the vicinity of 2.40-4.80 ppm of (a) and (b), respectively, that the diastereomers **6** and **10** are present in a ratio of at least 32:1.



6 **10**



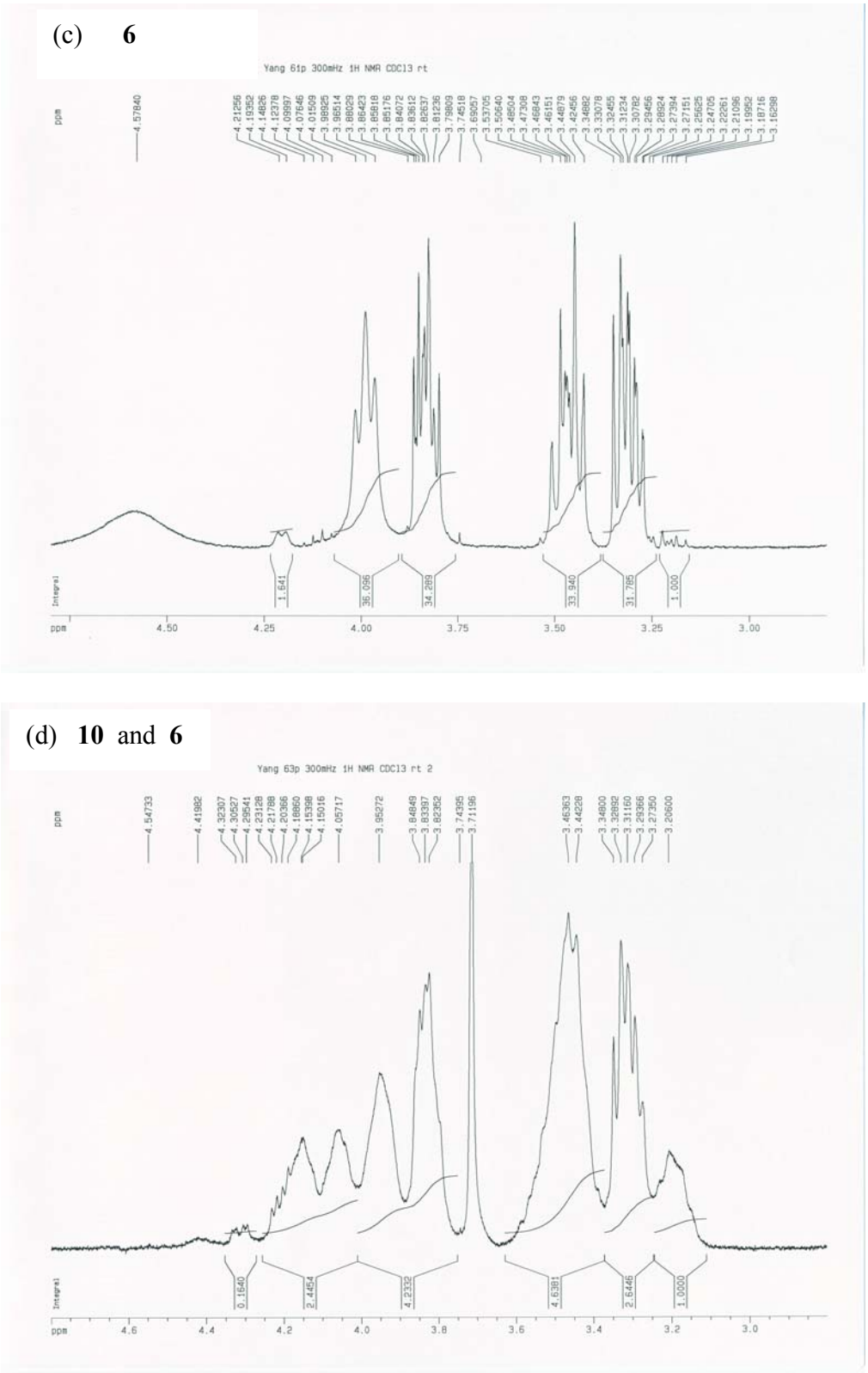
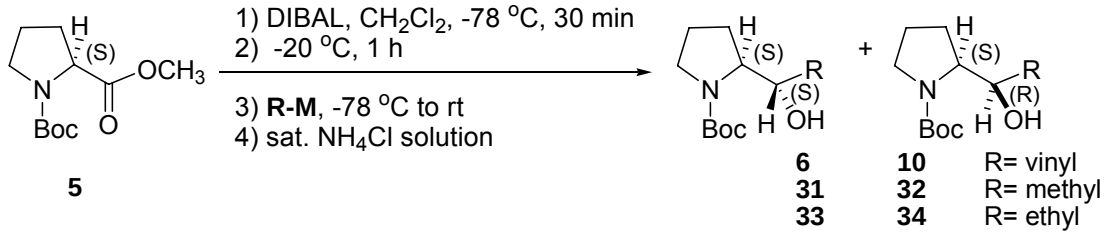


Figure 2.3 NMR spectra for diastereomers **6** and **10**

Taking advantages of the high selectivity and good yield of the advanced DIBAL reduction method, we synthesized several secondary amino alcohols by using different organometallic compounds in this reaction.

The diastereoselectivity of the reactions of *N*-Boc-*L*-proline methyl ester **5** with DIBAL and different organometallics was examined (Scheme 2.10). *N*-Boc protected β-amino alkanols (**6**, **10**, **31**-**34**) were isolated by quenching the reaction with saturated NH_4Cl solution. As shown in the table of Scheme 2.10, all of the organometallic compounds afforded high threo selectivity. The two by-products consisted of the erythro isomer and the primary alcohol from over-reduction. The yields (%) were the combined yields of both diastereomers, and the ratios were determined from the GC spectra of the crude products.



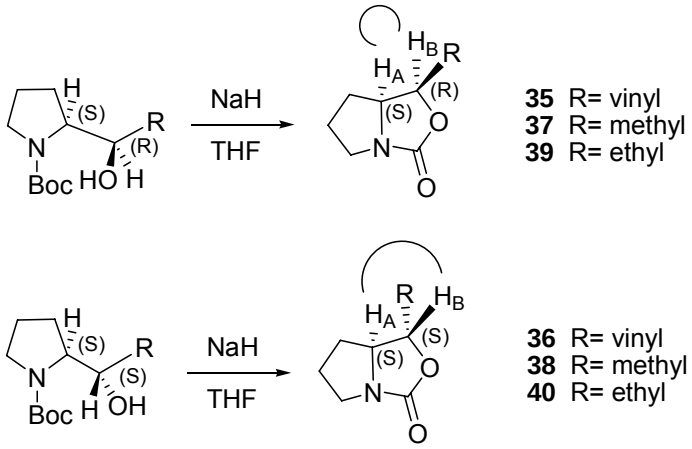
5

6 **10** R= vinyl
31 **32** R= methyl
33 **34** R= ethyl

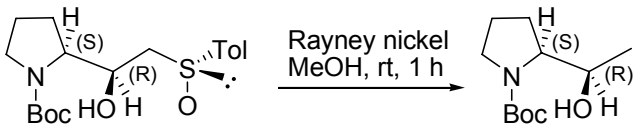
Entry	R	M	% Yield	Ratio
1	CH_2 =CH	MgBr	80	**6**:**10** > 32:1
2	CH_3	Li	49	**31**:**32** = 8:1
3	CH_2 CH_3	Li	52	**33**:**34** = 9:1
4	CH_3	MgBr	57	**31**:**32** = 6:1
5	CH_2 CH_3	MgBr	67	**33**:**34** = 28:1
6	$(CH_3)_2$	Zn	52	**31**:**32** = 10:1
7	$(CH_2$ $CH_3)_2$	Zn	54	**33**:**34** > 50:1
8	CH_3CH_2 CH_2	ZnCl	NA	No reaction

Scheme 2.10 Advanced ester reduction of *N*-Boc-*L*-proline methyl ester **5** followed by organometallic addition

The NMR spectra of diastereomers **6** and **10** are known.[3] The stereochemical assignments of these diastereomers were further confirmed by the ^{1}H-^{1}H NOESY NMR analysis of the oxazolidone derivatives obtained from a cyclization reaction (as shown in Scheme 2.11, R=vinyl).[3] For diastereomer **32**, prepared as in Scheme 2.12, the ^{1}H NMR and ^{13}C NMR data have been reported[46] but not the corresponding data for it diastereomer **31**. However, the ^{1}H NMR and ^{13}C NMR data of **37** and **38,** which are the corresponding cyclized products of **31** and **32**, are known.[48] With the ^{1}H NMR and ^{13}C NMR data of **37** and **38** available, the stereochemistry of both **31** and **32** could be readily deduced. The configurations of **33** and **34** were assigned based on NMR comparisons with diastereomers **31** and **32**, since their structures are very similar; the isomer with the lower field chemical shift for the methyl protons of the ethyl group is tentatively assigned as the threo isomer. This assignment also leads to the reasonable conclusion that the formation of the secondary alcohols **33** and **34** is analogous to those of **6** and **10** and of **31** and **32** by analogous processes.



Scheme 2.11 Stereochemical assignments for amino alcohols



41 **32**

Scheme 2.12 Literature synthesis of **32** from β- hydroxy sulfoxide **41**

In summary, the advanced DIBAL reductions on *N*-Boc-*L*-proline methyl ester **5** produced *N*-Boc protected β-amino secondary alcohols in very high diastereoselectivity and in good yield when organolithiums, Grignard reagents and dialkylzincs were used. A monoalkylzinc chloride does not bestow these benefits since it is apparently not as reactive as dialkylzinc reagents.

2.2.2. Mechanism study on advanced DIBAL reduction

It has been previously reported that there is better selectivity when advanced the ester reduction/alkylation is used rather than the addition of organometallics to the aldehydes.[3,6] In our current study, we also observed a high selectivity of advanced DIBAL reduction of *N*-Boc protected α-amino acid methyl ester **5** followed by the addition of organolithiums, Grignards, and dialkylzincs. However, the mechanism of this high selectivity is still obscure. In this part of the Chapter, our attempts to elucidate the mechanism from both experimental and theoretical perspectives are described.

First, we compared the ester reduction/alkylation method (without a warm-up step) with the advanced ester reduction/alkylation method (with a warm-up step). In Scheme 2.13, reaction (a) is the advanced ester reduction/alkylation with the warm-up step. *N*-Boc-*L*-proline methyl ester **5** was first mixed with DIBAL at -78 ^{o}C and the solution was then warmed to -20 ^{o}C for 1 h. The reaction mixture was then re-cooled to -78 ^{o}C before the addition of vinylmagnesium bromide. This experimental procedure gave a single diastereomer **6**. Reaction (b) is the basic

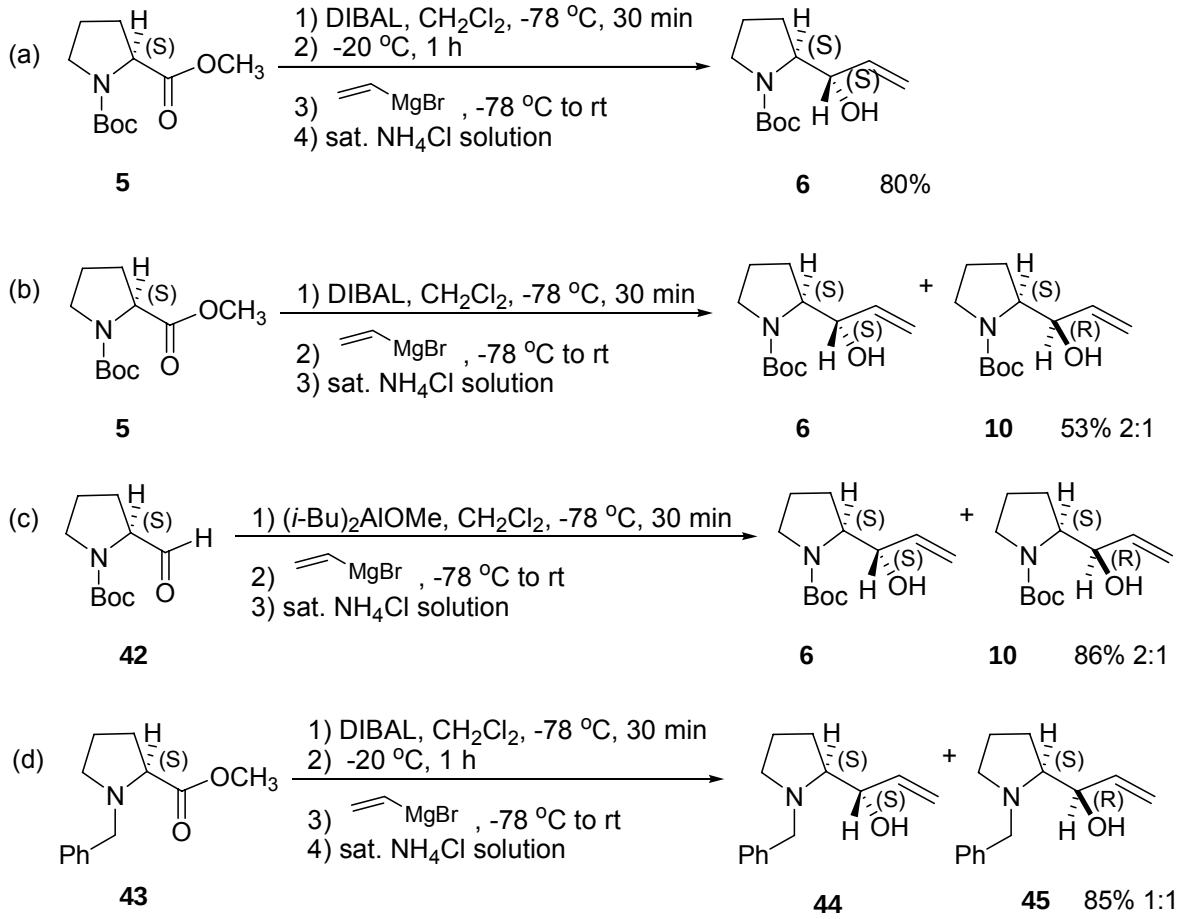
DIBAL reduction without the warm-up step. *N*-Boc-*L*-proline methyl ester **5** was added to DIBAL at -78 ^{o}C followed by the addition of vinylmagnesium bromide directly at -78 ^{o}C. The product was a 2:1 mixture of diastereomers **6** and **10**. This data indicates that the warm-up step, which is the only difference between reaction (a) and (b), is very likely the key to the high diastereoselectivity.

Two possible reaction mechanisms may be envisioned for the advanced ester reduction/alkylation. The first mechanism is that *N*-Boc-*L*-proline methyl ester **5** reacts with DIBAL to produce aluminoxy-acetals **R1** and **R2** (Figure 2.4). The higher temperature allows equilibration of **R1** and **R2**, leading to a very high ratio of **R1** to **R2**. Vinylmagnesium bromide then replaces the MeO group of **R1** with retention of configuration (S_Ni process) to give **6**. The second possible mechansim is the conversion of the aluminoxy-acetals **R1** and **R2** to an aldehyde and (*i*-Bu)$_2$AlOMe, and the addition of vinylmagnesium bromide to the aldehyde in the presence of (*i*-Bu)$_2$AlOMe. We set up a model reaction (as shown in reaction (c) in Scheme 2.13) to simulate the second predicted mechanism. *N*-Boc-*L*-prolinal **42** was mixed with (*i*-Bu)$_2$AlOMe at -78 ^{o}C and vinylmagnesium bromide was then added to the reaction mixture. This model reaction gave diastereomers **6** and **10** (2:1), suggesting that the second predicted mechanism involving an aldehyde intermediate is unlikely.

To experimentally determine that no aldehyde is involved in the mechanism, we tracked the warm-up step in reaction (a), Scheme 2.13, by NMR. In brief, *N*-Boc-*L*-proline methyl ester **5** was mixed with DIBAL in CD_2Cl_2 at -78 ^{o}C in an NMR tube. The NMR tube was sealed before it was placed in the NMR spectrometer. The NMR tube was warmed from -78 ^{o}C to -20 ^{o}C stepwise with increments of 15 ^{o}C; generally for each increment it took about 20 minutes to reach the higher temperature and another 15 minutes for temperature stabilization. At every 15

^{o}C increment, a proton NMR spectrum was collected. In all the spectra collected, no aldehyde peak around 10 ppm was found during the warm-up process from -78 ^{o}C to -20 ^{o}C. An extremely small aldehyde peak was observed after the reaction mixture had been maintained at -20 ^{o}C for 1 h. Based on this experimental data, we can be sure that no aldehyde is involved in the mechanism.

In the first predicted aluminoxy-acetal mechanism, aluminum can coordinate with an oxygen atom on the Boc group or with the nitrogen of the pyrrolidine ring. To test whether the Boc group is required, reaction (d) is Scheme 2.13 was designed in which the substrate bore an *N*-benzyl group instead of an *N*-Boc group. *N*-Benzyl-*L*-proline methyl ester **43** was first treated with DIBAL at -78 ^{o}C and then the mixture was warmed up to -20 ^{o}C and maintained at that temperature for 1 h. The reaction mixture was then re-cooled to -78 ^{o}C before the addition of vinylmagnesium bromide. This experimental procedure gave two diastereomers **44** and **45** in an approximate ratio of 1:1. By comparing reactions (a) and (d), we conclude that an oxygen atom on the Boc group probably plays an important role in the advanced DIBAL reaction with high diastereoselectivity. This concept is supported by the theoretical calculations that are discussed below.



Scheme 2.13 Mechanistic study on the advanced ester reduction/alkylation

Thus, the first aluminoxy-acetal mechanism is a reasonable one to explain the advanced DIBAL reduction reaction (a) in Scheme 2.13. As elucidated in detail in Figure 2.4, *N*-Boc-*L*-proline methyl ester **5** reacts with DIBAL and results in aluminoxy-acetal intermediates **R1** and **R2**. During the warm-up step, **R2** epimerizes to **R1**. When the reaction mixture is re-cooled to -78 °C, the aluminoxy-acetal **R1** undergoes an S_Ni reaction with vinylmagnesium bromide with retention of configuration to give **6** as the dominant diastereomer.

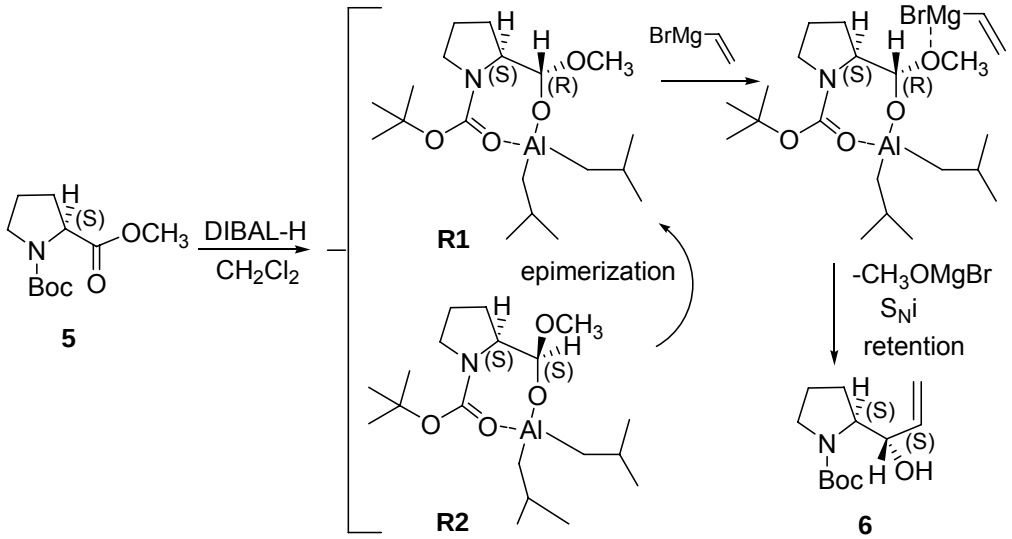


Figure 2.4 Postulated mechanism for the advanced ester reduction/alkylation of **5**

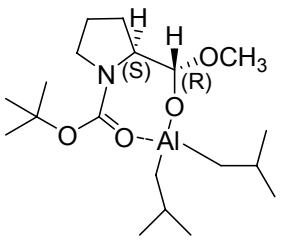
Theoretical calculations have been performed on the structure of the DIBAL adducts. It was postulated from evidence given above that the Al atom in the tetrahedral intermediates **R1** and **R2** is coordinated with the most basic and least crowded of the two oxygen atoms of the Boc group, the carbonyl oxygen atom. The computations were designed to determine if complexes **R1** and **R2** are reasonable structures for the DIBAL adducts and, if so, whether **R1** is substantially more thermodynamically stable than **R2**.

The theoretical calculations were done using Gaussian 03 software[49] with different semi-empirical and ab-initio methods. By using these methods, optimization of **R1** and **R2** was performed and the total energy and the optimized structures of **R1** and **R2** were studied.

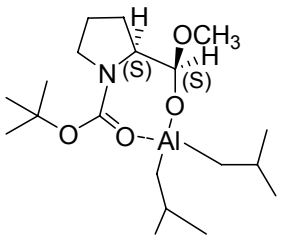
The methods used to optimize **R1** and **R2** include semi-empirical methods, such as AM1 and PM3, and ab-initio methods, such as HF (Hartree-Fork) 3-21G*, DFT (density function theory) B3LYP/6-31G*, B3LYP/6-31+G*, B3LYP/6-31++G**, B3LYP/Gen and ONIOM (B3LYP/6-31++G**:B3LYP/6-31G*). A series of "standard" basis sets is stored internally in Gaussian; these basis sets may be specified by including the appropriate keyword within the

route section for the calculation. The Gen keyword allows a user-specified basis set to be used in the Gaussian calculation. In the ONIOM procedure, the molecular system being studied is divided into two or three layers which are treated with different model chemistries. The results are then automatically combined into the final predicted results. Layer assignments are specified as part of the molecule specification.

Density function theory (DFT) was found to be the most time expensive but the best calculation method compared to semi-empirical methods (AM1 and PM3) and Hartree-Fock theory. Many published reports use density function theory for their theoretical calculations, especially for organic chemistry. It is the method we finally adopted for our theoretical calculations. As shown in Table 2.1, the results calculated by different methods agree with each other, and all of them suggest that the total energy of **R2** is higher than **R1**. Using method B3LYP/6-31+G*, the total energy of **R2** is 6.017 kcal/mol higher than **R1**, a decisive difference.



R1



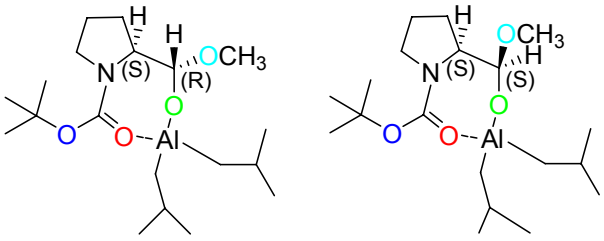
R2

	Total energy (H) 1 H = 627.51 kcal/mol	Energy difference R1-R2 (kcal/mol)
R1_AM1_G	-0.41254	-3.53511
R2_AM1_G	-0.40691	
R1_PM3_G	-0.41240	-6.09923
R2_PM3_G	-0.40268	
R1_HF3-21G*_G	-1330.31620	-9.20351
R2_HF3-21G*_G	-1330.30153	
R1_DFT6-31G*_G	-1345.12318	-5.659412
R2_DFT6-31G*_G	-1345.11416	
R1_DFT6-31+G*_G	-1345.15546	-6.01734
R2_DFT6-31+G*_G	-1345.14587	
R1_ONIOM	-1345.20675	-5.24441
R2_ONIOM	-1345.19840	
R1_Gen	-1345.20828	-6.04725
R2_Gen	-1345.19864	

Table 2.1 Total Energies of **R1** and **R2** calculated by different methods

In the optimized structures of **R1** and **R2**, the distances between the aluminum atom and the four oxygen atoms were measured. As shown in Table 2.2, calculations by all of the different methods indicate that the Al-O bond distance is around 1.80 Å and the distance between the Al and the carbonyl oxygen atom of the Boc group is around 1.95 Å, except that in the semiempirical methods it is 2.4-2.5 Å in the case of R1; such a distance indicates coordination between the Al and this oxygen atom. On the other hand, the distances between Al and the oxygen atoms on the methoxy group and the butoxy group in Boc are around 3.8-4.0 Å,

suggesting that no coordination exists. Therefore, the calculation results tell us that the Al atoms in **R1** and **R2** bonds with the O atom on the stereo center and coordinates with the carbonyl O on the Boc group, to form the aluminoxy-acetal.



R1 **R2**

	Al-O(carbonyl on Boc) length (Å)	Al-O bond length (Å)	Al-O (OMe) length (Å)	Al-O (on Boc) length (Å)
R1_AM1_G	2.41365	1.74494	3.82501	4.46249
R2_AM1_G	1.83017	1.77085	3.76605	3.88320
R1_PM3_G	2.45997	1.76147	3.61861	4.67955
R2_PM3_G	1.86865	1.79708	3.61433	4.05575
R1_HF_G	1.87222	1.74815	3.80520	4.06886
R2_HF_G	1.88299	1.76116	3.95279	3.92682
R1_DFT6-31+G*_G	1.94888	1.78720	3.63919	4.12067
R2_DFT6-31+G*_G	1.95960	1.79390	3.92336	3.99970
R1_ONIOM	1.94649	1.78762	3.78663	4.13982
R2_ONIOM	1.96418	1.79763	3.93527	4.0157
R1_Gen	1.94949	1.78871	3.63171	4.11993
R2_Gen	1.96056	1.7954	3.92392	4.00130

Table 2.2 Distances between Al atom and O atoms in **R1** and **R2**

As presented in Figure 2.5, the distances between the corresponding Al atoms and oxygen atoms measured from the crystal structures of many tetra-coordinated aluminum compounds are in excellent agreement with those determined from our theoretical calculations.[50] This agreement gives us confidence in the reliability of our calculation.

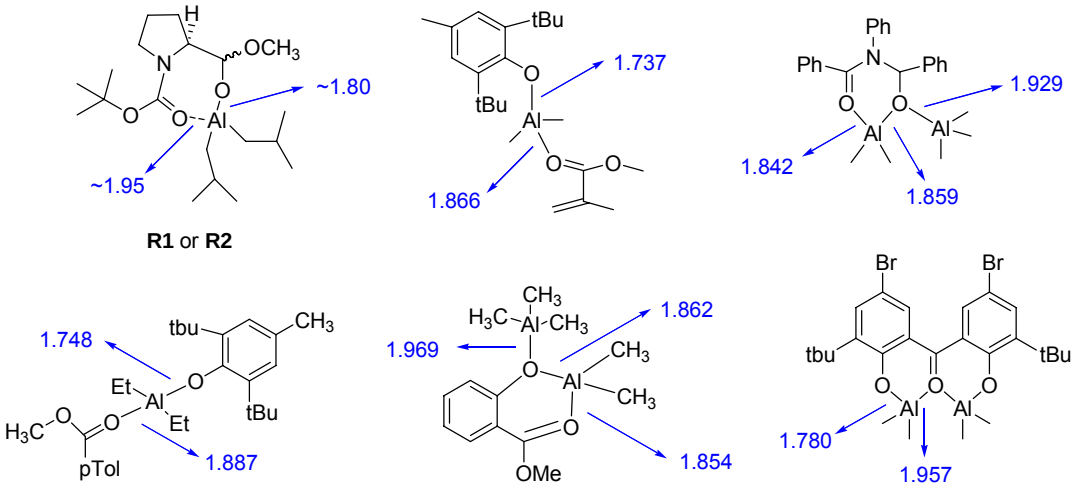
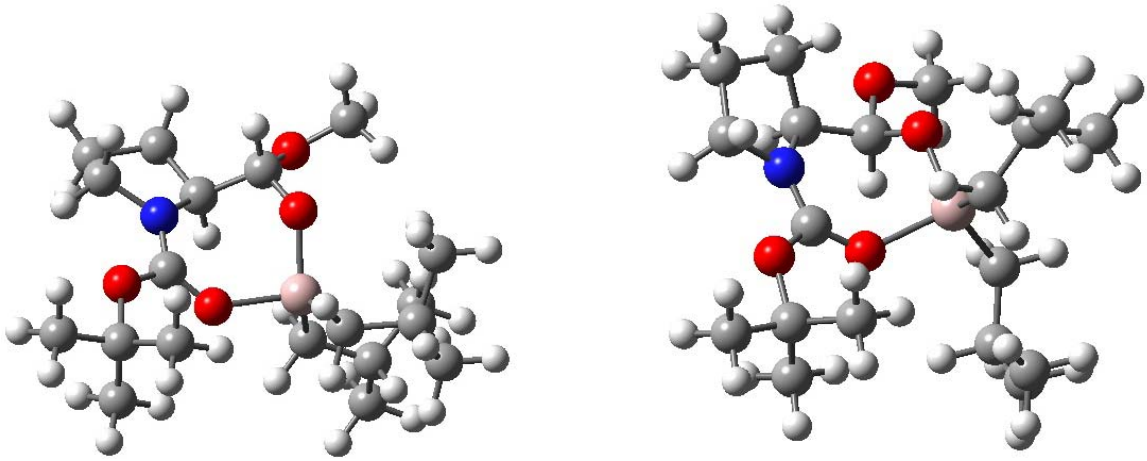


Figure 2.5 Crystal structure data of tetra-coordinated aluminium compounds

Figure 2.6 shows the conformations of **R1** and **R2** after they were optimized by B3LYP/6-31+G*. Thus, as suggested in our original hypothesis, the main intermediates are probably also fused 5- and 7-membered rings.



R1 **R2**

Figure 2.6 **R1** and **R2** optimized by B3LYP/6-31+G*

It is known that Al can undergo tetra-coordination and penta-coordination as well as hexa-coordination.[50] To test whether there is a higher degree of coordination in **R1** or **R2** than 4, we

attempted to form a penta-coordinated structure (with O of the butoxy group in Boc or of the methoxy group). Pre-formed penta-coordination structures of **R1** or **R2** were optimized by AM1 and PM3. Table 2.3 shows the energy and structure data after optimization. In all cases, the penta-coordination was broken up during the optimization process and the resulting conformations had energies higher than those associated with tetra-coordination. Based on this data, we can conclude that penta-coordination does not exist in **R1** and **R2**.

	Total energy (kcal/mol)	Al-O(cabonyl on Boc) length (Å)	Al-O bond length (Å)	Al-O (OMe) length (Å)	Al-O (on Boc) length (Å)	Energy difference R1-R2 (kcal/mol)
R1_AM1_pentaBoc	-246.24734	3.80323	1.74407	3.781	2.489	10.0250
R2_AM1_pentaBoc	-256.27232	2.43567	1.75016	3.630	4.289	
R1_AM1_pentaOMe	-258.87453	2.41363	1.74494	3.825	4.462	-2.6311
R2_AM1_pentaOMe	-256.24343	2.43567	1.75016	3.630	3.883	
R1_PM3_pentaBoc	-236.62970	4.22043	1.75830	3.601	2.532	9.6340
R2_PM3_pentaBoc	-246.26372	2.47137	1.77524	3.616	2.556	
R1_PM3_pentaOMe	-251.56474	2.55690	1.75114	2.646	4.835	0.4266
R2_PM3_pentaOMe	-251.99134	2.54561	1.74876	2.639	4.809	

Table 2.3 The energy and structure data of penta-coordinated structures for **R1** or **R2** after optimization

To reveal the structural basis for the energy difference of **R1** and **R2**, calculations were performed on simplified structures in which the isobutyl groups of **R1** and **R2** were replaced by hydrogens, (**H1**, **H2** in Figure 2.7) and by methyl groups (**M1**, **M2** in Figure 2.7) and the structures were optimized by the same method (B3LYP/6-31+G*) used for **R1**, **R2** optimization. Figure 2.8 shows the conformations of **M** and **H** after optimization by B3LYP/6-31+G*. All optimized **M** and **H** structures are aluminoxy-acetals in accord with the data from **R**.

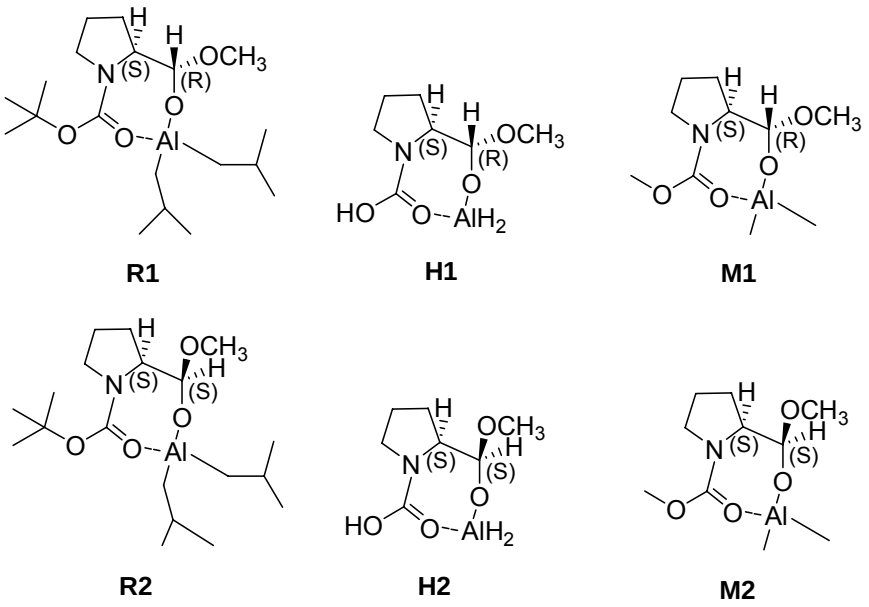
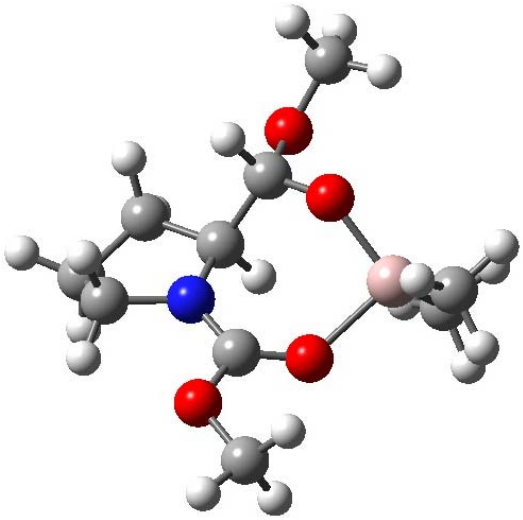
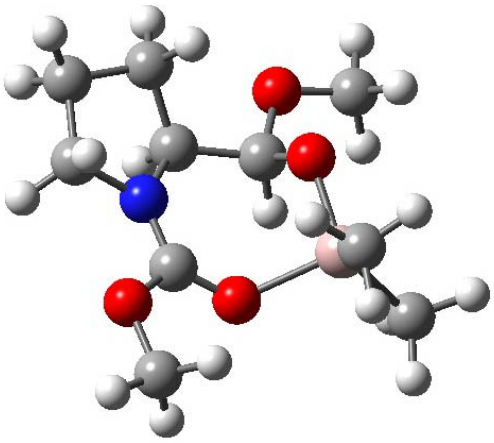


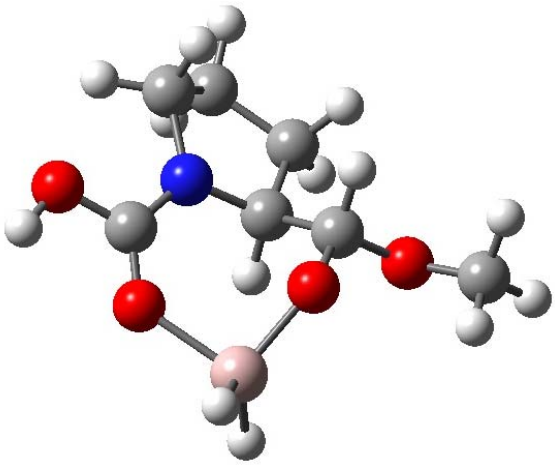
Figure 2.7 Structures of **H** (**H1** or **H2**), **M** (**M1** or **M2**) and **R** (**R1** or **R2**)



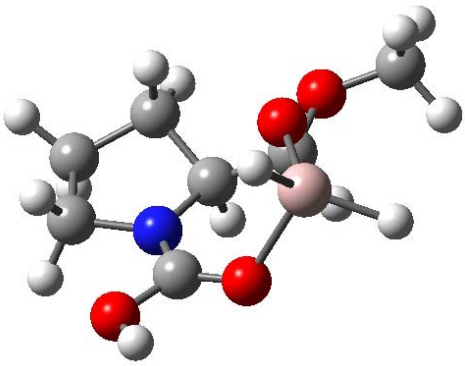
M1



M2



H1



H2

Figure 2.8 **M** (**M1** or **M2**) and **H** (**H1** or **H2**) optimized by B3LYP/6-31+G*

Tables 2.4 and 2.5 show the free energy and structure data of the optimized **M** (**M1**, **M2**), **H** (**H1**, **H2**), **R1** and **R2**. The free energy difference between **M1** and **M2**, **H1** and **H2**, and **R1** and **R2** are -5.19 kcal/mol, -4.48 kcal/mol and -5.64 kcal/mol respectively. The energy differences within **M** (**M1** or **M2**), **H** (**H1** or **H2**) and **R** (**R1** or **R2**) are remarkably close to each other and the nature of the two substituents on Al thus has very little influence on the energy difference between the two diastereomers. Therefore, the energy difference between the two diastereomers

R1 and **R2** is probably due to interactions between groups on the 7-membered rings bearing the Al. There is no obvious crowding between the MeO group and the hydrogens on the 3 methylene group in *trans* isomer R2. (see Appendix B)

	Energy H	Zero-point correction H/particle	Sum of electronic and thermal free energies H (T= -20 °C, 253 K)	ΔG(R1-R2) kcal/mol
R1	-1345.15546	0.55650	-1344.662958	-5.64320
R2	-1345.14587	0.55661	-1344.653965	
H1	-873.36520	0.21596	-873.189492	-4.47503
H2	-873.35810	0.21619	-873.181922	
M1	-991.32719	0.30140	-991.074073	-5.19390
M2	-991.31959	0.30162	-991.065796	

Table 2.4 Free energies of the optimized **M**, **H** and **R** by B3LYP/6-31+G*

	Al-O(cabonyl on Boc) length (Å)	Al-O bond length (Å)	Al-O (OMe) length (Å)	Al-O (on Boc) length (Å)
R1	1.94888	1.78720	3.63919	4.12067
R2	1.95960	1.79390	3.92336	3.99970
H1	1.94413	1.78053	3.60887	4.07657
H2	1.94954	1.78851	3.88375	3.84009
M1	1.95294	1.78785	3.63404	4.08154
M2	1.96272	1.79532	3.91362	3.9657

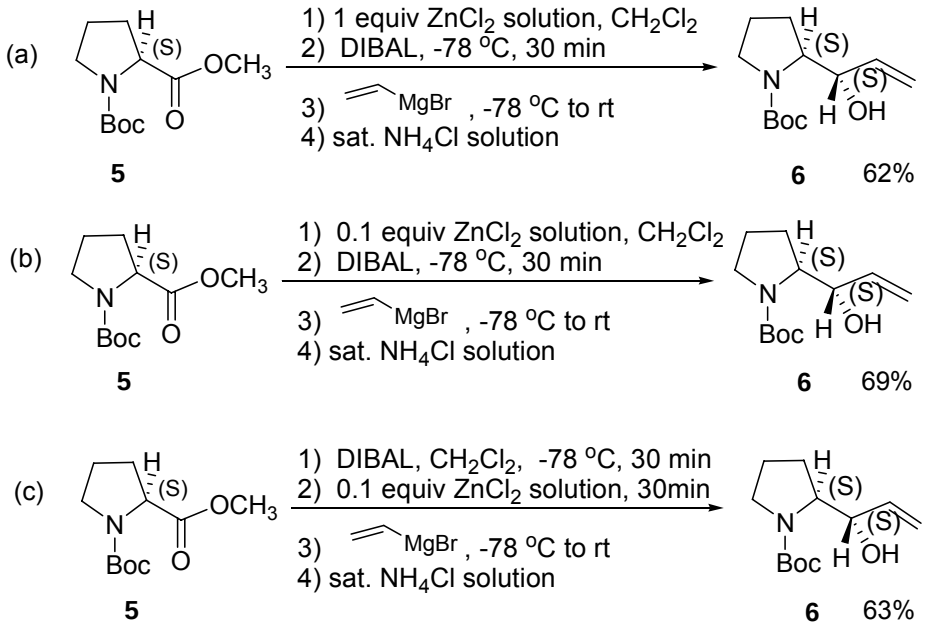
Table 2.5 Distances between Al atom and O atoms in **M**, **H** and **R** by B3LYP/6-31+G*

2.2.3. Improvement in the advanced ester reduction/alkylation method

In this advanced ester reduction/alkylation mechanism, which was first proposed based on experimental data and later confirmed by theoretical calculations, we found that the existence of an equilibration between the reaction intermediates is the key to the high reaction stereoselectivity. Any factor affecting the equilibration may also affect this selectivity. A warm-

up step was applied in our previous study and the higher temperature indeed increased the selectivity. However, a warm-up step is time consuming and requires careful temperature control. In an attempt to discover a simpler method than the warm-up step, we have utilized $ZnCl_2$ in the ester reduction/alkylation in the hope that this Lewis acid would help remove the MeO group and allow the methoxy group to be re-deposited on the other side of the 7-memered ring, thus facilitating the epimerization.

As described in reaction (a) in Scheme 2.14, DIBAL was added to the mixture of *N*-Boc-*L*-proline methyl ester **5** and 1 equiv $ZnCl_2$, followed by adding vinylmagnesium bromide. The reaction did indeed produce a single diastereomer **6**. Furthermore, this reaction also worked well with a catalytic amount $ZnCl_2$ and yielded a single diastereomer **6**, as shown in reaction (b) Scheme 2.14. This reaction is of significant mechanistic and practical importance. First, it significantly simplifies the reaction but still maintains the high selectivity. Second, it strongly supports the mechanism that we advocate. To ensure that the high selectivity originated from the effect of $ZnCl_2$ on the equilibration, but not from the $ZnCl_2$ causing chelation between the oxygen or nitrogen atoms inducing selectively in the DIBAL addition step, reaction (c) in Scheme 2.14 was performed. After DIBAL was added to *N*-Boc-*L*-proline methyl ester **6**, 0.1 equiv $ZnCl_2$ was added to the reaction mixture, followed by the addition of vinylmagnesium bromide. Reaction (c) indeed affords one single diastereomer **6**. Therefore, reaction (a), (b) and (c) provide solid evidence for our suggested mechanism.



Scheme 2.14 Advanced ester reduction/alkylation with Lewis acid catalyzed equilibration

2.3. Conclusions

The addition of vinylmagnesium bromide to the DIBAL adduct of *N*-Boc-*L*-proline methyl ester, after a warm-up step, gives a Boc-protected β-amino secondary allylic alcohol with high diastereoselectivity of greater than 32:1. This method can be expanded to other Grignard reagents, organolithiums and dialkylzincs with slightly less stereoselectivity.

N-Boc-*L*-proline methyl ester reacts with DIBAL to produce aluminoxy-acetals **R1** and **R2**. The higher temperature probably causes equilibration of **R1** and **R2**, leading to a very high ratio of **R1** to **R2**. The ratio is consistent with the high computed energy differences between **R1** and **R2** and favoring the former. Vinylmagnesium bromide then reacts with **R1** to cause replacement of the methoxide ion with the vinyl nucleophile with retention of configuration (S_Ni process) and gives the protected β-amino secondary allylic alcohol **6**.

Adding $ZnCl_2$ before or after the addition of DIBAL, followed by vinylmagnesium bromide, significantly simplifies the reaction allowing one to avoid the warm-up step, which is time consuming and requires careful temperature control. The high stereoselectivity is still maintained. The Lewis acid $ZnCl_2$ is postulated to aid the removal of the MeO group; this group may be re-deposited on the other side of the 7-memered ring, thus facilitating the epimerization.

2.4. Experimental

General Considerations: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shift data are reported in units of δ (ppm) relative to $CHCl_3$ as δ = 7.26 for ^{1}H NMR spectra and $CDCl_3$ as δ = 77.09 for ^{13}C NMR spectra. Multiplicities are given as: s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hz and refer to apparent peak multiplicities and not true constants. Silica gel 60 (40-60 μm, Sorbent Technologies) was used for flash column chromatography. Thin-layer chromatography was performed on glass supported 250-μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light; 7% phosphomolybdic acid in ethanol; 5% anisaldehyde in ethanol containing 5% sulfuric acid and a trace amount of acetic acid. The ratios between diastereomers were determined by ^{1}H NMR spectroscopy and/or GC analysis. GC analyses were carried out with the Agilent 6850 Series GC System by using the Agilent 19091Z-413E HP-1 methyl siloxane column, heated from 50 ^{o}C to 315 ^{o}C with a rate of 10 ^{o}C/min, and were detected by FID. Anhydrous magnesium sulfate was used as the drying reagent. All reactions were performed under an argon atmosphere and standard precautions against moisture were taken. A Dry Ice/acetone bath was used to obtain a temperature of -78 ^{o}C and -20 ^{o}C. An ice bath was used to obtain 0 ^{o}C. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium benzophenone ketyl. Hexane was distilled over sodium hydride and toluene was distilled from sodium. All reagents used were purchased from Aldrich.

(*S*)-1-*tert*-butyl 2-methylpyrrolidine-1,2-dicarboxylate (5).[44] A solution of (0.59 g, 5.1 mmol) of *L*-proline in 5 mL of methanol was cooled to 0 ^{o}C and thionyl chloride (0.40 mL, 5.5

mmol) was added dropwise over 20 min. After the solution had been refluxed for 1 h, the solvent was removed in vacuo to afford a yellow oil which was then dissolved in 6 mL of CH_2Cl_2 under argon before triethylamine (1.03 g, 1.4 mmol) and di-*tert*-butyl dicarbonate (1.33 g, 6.1 mmol) were added at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 1 h and then at room temperature overnight. It was made acidic by adding saturated citric acid solution. The organic layer was separated and washed with H_2O, saturated $NaHCO_3$ and then brine. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil that was purified by column chromatography (15% acetone in hexanes) to yield 0.99 g (85%) of the title product as a yellow oil. ^1H NMR ($CDCl_3$) δ 4.27 (dd, J=8, 4 Hz, 0.5 H), 4.17 (dd, J=8, 5 Hz, 0.5 H), 3.68 (s, 3 H), 3.51-3.32 (m, 2 H), 2.18 (m, 1 H), 1.87 (m, 3 H), 1.41 (s, 3.7 H), 1.36 (s, 6.6 H); ^{13}C NMR ($CDCl_3$) δ 173.67, 173.42, 154.33, 153.69, 79.73, 59.00, 58.62, 51.98, 51.82, 46.45, 46.21, 30.78, 29.81, 28.22, 24.24, 23.59; $[\alpha]_{589}$ = -65.5 (c=0.44, MeOH).

(*S*)-*tert*-butyl 2-((*S*)-1-hydroxyallyl)pyrrolidine-1-carboxylate (6) and (*S*)-*tert*-butyl 2-((*R*)-1-hydroxyallyl)pyrrolidine-1-carboxylate (10)

Procedure (a) :[4,6] Ester reduction/alkylation method.

DIBAL (2.62 mL of a 1.0 M solution in hexane, 2.62 mmol) was added to a solution of *N*-Boc-proline methyl ester **5** (0.50 g, 2.18 mmol) in CH_2Cl_2 (10 mL) at -78 ^oC. The resulting solution was stirred at -78 ^oC for 30 min, followed by the addition of vinylmagnesium bromide (6.54 mL of a 1.0 M solution in THF, 6.54 mmol) dropwise at -78 ^oC. The solution was then allowed to slowly warm to room temperature overnight. Saturated aqueous NH_4Cl solution (10 mL) was added to quench the reaction. Saturated sodium tartrate solution (10 mL) was added to resulting gel. The mixture was stirred at room temperature for 30 min. The organic layer was

extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an inseparable mixture of diastereomers **6** and **10** at 2:1 ratio. Flash chromatography (30% ethyl acetate in hexanes) gave 0.26 g of the title compound (yield 53%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 1 H), 5.33-5.16 (m, 2 H), 4.12 (m, 0.67 H), 3.92 (m, 1.33 H), 3.45 (m, 1 H), 3.31 (m, 0.7 H), 3.21 (m, 0.3 H) 1.90-1.68 (m, 4 H), 1.47 (s, 6 H), 1.46 (s, 3H).

Procedure (b):[4,6] Advanced ester reduction/alkylation method.

DIBAL (2.62 mL of a 1.0 M solution in hexane, 2.62 mmol) was added to a solution of *N*-Boc-*L*-proline methyl ester **5** (0.50 g, 2.18 mmol) in CH_2Cl_2 (10 mL) at -78 ^{o}C. The resulting solution was stirred at -78 ^{o}C for 30 min, and then at -20 ^{o}C for 1 h. The mixture was re-cooled to -78 ^{o}C, followed by the dropwise addition of vinylmagnesium bromide (6.54 mL of a 1.0 M solution in THF, 6.54 mmol). The solution was then allowed to slowly warm to room temperature overnight. Saturated aqueous NH_4Cl (10mL) solution was added to quench the reaction. Saturated sodium tartrate solution (10 mL) was added to the resulting gel and the mixture was stirred at room temperature for 30 min. The organic layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (30% ethyl acetate in hexanes) gave 0.40 g of the title compound (yield 80%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.81 (m, 1 H), 5.31 (d, J=17 Hz, 1 H), 5.18 (d, J=10 Hz, 1 H), 4.00 (m, 1 H), 3.85 (m, 1 H), 3.49 (m, 1 H), 3.29 (m, 1 H), 1.90-1.69 (m, 4 H), 1.48 (s, 9 H); ^{1}H NMR (C_6D_6) δ 5.77 (m, 1 H), 5.35 (m, 1 H), 5.06 (d, J=10 Hz, 1 H), 4.11 (m, 1 H), 3.82 (m, 1 H), 3.17 (m, 1 H), 3.00 (m, 1 H), 1.47-1.20 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 157.85, 138.33, 116.69, 80.43, 77.21, 62.39, 47.32, 29.62, 28.38 (3 C), 23.80; ^{13}C NMR (C_6D_6) δ 157.13, 138.96, 115.92, 79.88, 75.91, 62.84, 47.49, 28.46 (3 C), 27.56, 24.05.

Procedure (c):[4,6] Addition of vinylmagnesium bromide to *N*-Boc-*L*-prolinal in the presence of (*i*-Bu)$_2$AlOMe.

Dry methanol (0.02 mL, 0.52 mmol) was added to DIBAL (0.52 mL of a 1.0 M solution in hexane, 0.52 mmol) at -78 ^{o}C. The resulting mixture was stirred at -78 ^{o}C for 30 min, followed by the addition of a solution of *N*-Boc-*L*-prolinal **42** (0.10 g, 0.44 mmol) in CH_2Cl_2 (4 mL). Vinylmagnesium bromide (1.32 mL of a 1.0 M solution in THF, 1.32 mmol) was then added to the mixture dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature overnight. Saturated aqueous NH_4Cl solution was added to quench the reaction. Saturated sodium tartrate solution (8 mL) was added to the resulting gel and the mixture was stirred at room temperature for 30 min. The organic layer was extracted with CH_2Cl_2 (3 x 10mL) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an inseparable mixture of diastereomers **6** and **10** at 2:1 ratio (0.085 g, 86%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 1 H), 5.33-5.16 (m, 2 H), 4.12 (m, 0.67 H), 3.92 (m, 1.33 H), 3.45 (m, 1 H), 3.28 (m, 0.6 H), 3.21 (m, 0.3 H) 1.90-1.68 (m, 4 H), 1.47 (s, 6 H), 1.46 (s, 3H).

Procedure (d): With the use of $ZnCl_2$ catalysis of equilibration instead of warming.

DIBAL (0.48 mL of a 1.0 M solution in hexane, 0.48 mmol) was added to a solution of *N*-Boc-*L*-proline methyl ester **5** (0.10 g, 0.44 mmol) and $ZnCl_2$ (0.44 mL of a 1.0 M solution in ether, 0.44 mmol) in CH_2Cl_2 (2 mL) at -78 ^{o}C. The resulting solution was stirred at -78 ^{o}C for 30 min, followed by the addition of vinylmagnesium bromide -78 ^{o}C (1.31 mL of a 1.0 M solution in THF, 1.31 mmol) dropwise. The solution was then allowed to warm to room temperature overnight. Saturated aqueous NH_4Cl solution was added to quench the reaction. Saturated sodium tartrate solution (3 mL) was added to the resulting gel and the mixture was stirred at

room temperature for about 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo to give crude product as a yellow oil. Flash chromatography (30% ethyl acetate in hexanes) gave 0.057 g of the title compound (yield 62%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.84 (m, 1 H), 5.30 (d, J= 13 Hz, 1 H), 5.18 (d, J=10 Hz, 1 H), 3.98 (m, 1 H), 3.85 (m, 1 H), 3.48 (m, 1 H), 3.31 (m, 1 H), 2.04-1.72 (m, 4 H), 1.47 (s, 9 H).

Analogous experiment were performed in which only 10% of $ZnCl_2$ was used (i) before addition of DIBAL and (ii) after the addition of DIBAL and the results were virtually the same.

(*S*)-tert-butyl 2-((*S*)-1-hydroxyethyl)pyrrolidine-1-carboxylate (31) and (*S*)-tert-butyl 2-((*R*)-1-hydroxyethyl)pyrrolidine-1-carboxylate (32).[46] The procedure was the same as for **6** and **10** except that methylmagnesium bromide or methyl lithium or dimethyl zinc was used instead of vinylmagnesium bromide. It gave 0.54 g (57%) **31** and **32** at 6:1 ratio when methylmagnesium bromide was used. It gave 0.46 g (49%) **31** and **32** at 8:1 ratio when methyl lithium was used. It gave 0.49 g (52%) **31** and **32** at 10:1 ratio when dimethyl zinc was used. ^{1}H NMR ($CDCl_3$) δ 5.19 (br, 1 H), 3.74-3.65 (m, 2 H), 3.47 (m, 1 H), 3.25 (m, 1 H), 2.00 (m, 1 H), 1.89-1.70 (m, 2 H), 1.59 (m, 1 H), 1.47 (s, 9 H), 1.14 (d, J=6 Hz, 3 H).

(1*S*,7*aS*)-1-methyl-tetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-one (38).[3] **31** (0.089 g, 0.41 mmol) in THF (4 mL) was treat with NaH (0.033 g of 60% wt dispersed in mineral oil, 0.83 mmol) at 0 ^{o}C. The suspension was stirred at 0 ^{o}C for 5 min, and then at room temperature overnight. The reaction was quenched with H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL) the combined organic extract was dried over anhydrous $MgSO_4$ and

concentrated in vacuo. Flash chromatography (50% ethyl acetate in hexanes) gave 0.040 g of the title compound (yield 69%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 4.0 (m, 1 H), 3.63 (m, 1 H), 3.49 (m, 1 H), 3.15 (m, 1 H), 2.12-1.82 (m, 4 H), 1.48-1.46 (d, J=6.4 Hz, 3 H); ^{13}C NMR (C_6D_6) δ 160.97, 75.98, 65.67, 45.83, 30.17, 25.51, 21.06.

(*S*)-methyl 1-benzylpyrrolidine-2-carboxylate (43). A mixture of *L*-proline methyl ester hydrochloride (0.30 g, 1.78 mmol), benzyl bromide (0.30 g, 1.8 mmol) and K_2CO_3 (0.98 g, 7.1 mmol) in dry CH_2Cl_2 was stirred at room temperature for 24 h. The reaction mixture was poured into a mixture of water (5 mL) and ethyl acetate (10 mL). The aqueous layer was washed with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (15% ethyl acetate in hexanes) gave 0.28 g of the title compound (yield 69%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.41-7.35 (m, 5 H), 3.97 (d, J=13 Hz, 1 H), 3.73 (s, 3 H), 3.66 (d, J=13 Hz, 1 H), 3.33 (m, 1 H), 3.17-3.12 (m, 2 H), 2.28-1.26 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 174.46, 138.36, 129.12, 128.10, 127.01, 65.22, 58.60, 53.16, 51.55, 29.32, 22.98.

3. ASYMMETRIC SYNTHESIS METHOD FOR NITROGEN HETEROCYCLES

3.1. Introduction

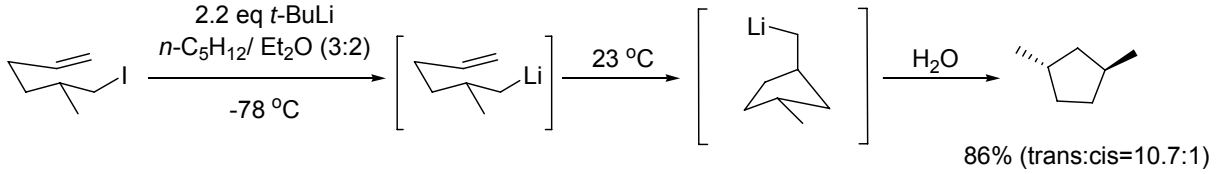
3.1.1. Background for methods to produce organolithiums by intramolecular carbolithiation

There have been an increasing number of papers about the intramolecular addition of alkyllithiums to unactivated alkenes as a preparative method for cyclopentylmethyllithiums, their heterocyclic analogues and, less effectively, the corresponding six-membered rings.[51-53] Although recent significant advances has been made by many in this field, the methods to produce organolithiums by intramolecular carbiolithiation still have considerable limitations. Previously, a major limitation has been the lack of a general method for preparing organolithiums. For the most part, the conventional generation methods can only be used for primary organolithiums or those with special stabilizing features such as adjacent heteroatom groups that direct lithiations or sp^2 character of the carbon atom bearing the lithium. In most cases, the organolithium was produced by halogen-lithium or tin-lithium exchange or by heteroatom-directed lithiation.

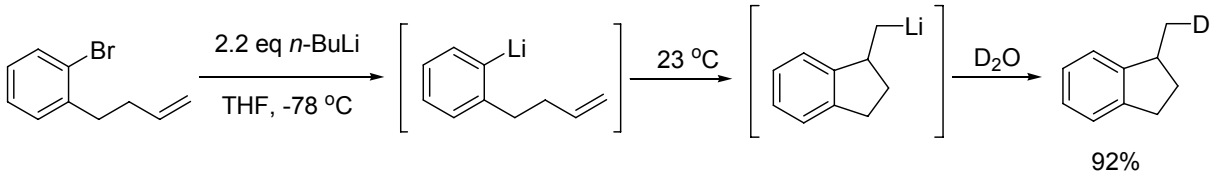
Halogen-lithium exchange is a method to generate primary alkyllithiums, aryllithiums, and vinyllithiums, which can undergo intramolecular carbolithiation (Scheme 3.1). All three reactions[54-56] in Scheme 3.1 give cyclized products in good yield. Reaction (a)[57,58] has become a standard method to generate primary alkyllithiums and is widely used in organic synthesis.

These organolithiums could be formed at -78 °C. However, the carbolithiation reaction requires a higher temperature, such as 0 °C or ambient temperature.

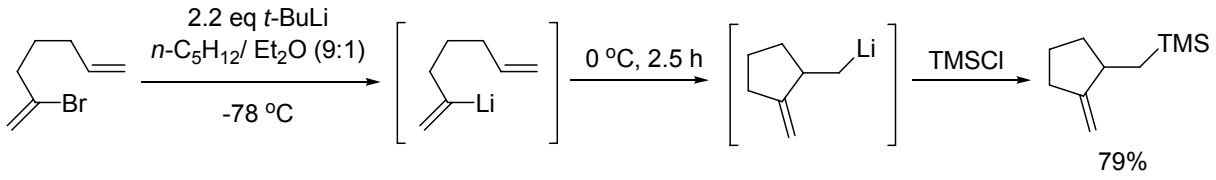
(a) Primary alkyllithium cyclization



(b) Arylithiums cyclization



(c) Vinyllithium cyclization



Scheme 3.1 Intramolecular carbolithiation by halogen-lithium exchange

The mechanism of halogen-lithium exchange (Scheme 3.2) involves a step proceeding through an ate-complex intermediate.[59] Two equivalents of *t*-BuLi are needed for the reaction. The first equivalent of *t*-BuLi reacts with the alkyl iodide **46** to form an ate-complex **47**, which decomposes to *t*-BuI and the alkyllithium **48**. The first two reactions are reversible. The second equivalent of *t*-BuLi reacts with *t*-BuI and drives the equilibra to the alkyllithium product side. A limitation of halogen-lithium exchange is that secondary and tertiary alkyllithiums can not be formed through halogen-lithium exchange due to the severe Wurtz-type coupling and elimination reactions of secondary and tertiary halides.