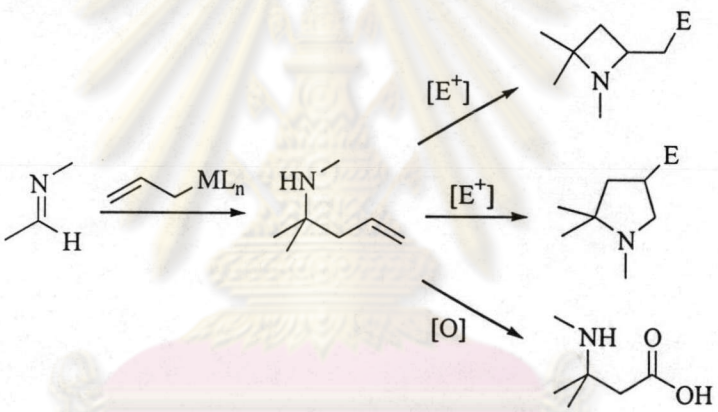
CHAPTER III

RESULTS AND DISCUSSION

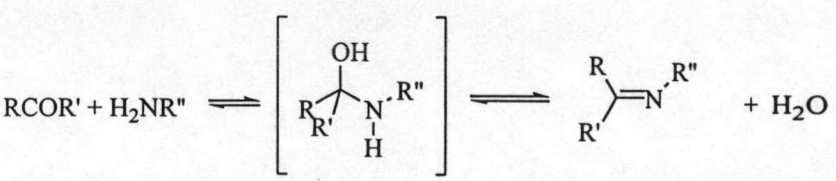
The objective of this research is to develop a synthetic method involving nucleophilic addition of carbon nucleophiles to imines. The carbon nucleophile used in this study is an allylindium reagent formed *in situ* form allyl bromide and indium metal. The substrates chosen are unactivated *N*-alkyl aldimines which are known to be quite difficult for such reactions. The resulting homoallylic amines are potentially useful starting materials for synthesis of bioactive natural products such as pyrolidine alkaloids, azetidine alkaloids and β-amino acids (**Scheme 3.1**).



Scheme 3.1

3.1 The synthesis of imines

Imines are generally synthesized from the reaction of aldehydes or ketones with amines (**Scheme 3.2**).[35] This reaction was first discovered by Schiff in 1864, therefore imines are often referred to as Schiff bases.



Scheme 3.2

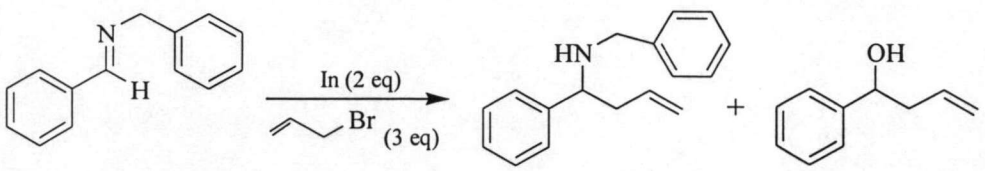
The reaction is acid-catalyzed. The acid protonates the carbonyl group to give a carbenium ion which was attacked by the amine. A drying agent such as anhydrous magnesium sulfate or molecular sieve is generally added to ensure the forward equilibrium. All imines used in this study were prepared by mixing an equimolar amount of the amine and aldehyde in the presence of anhydrous magnesium sulfate in dichloromethane at room temperature overnight. Filtration followed by evaporation of the solvent gave the imines which were characterized by sharp singlet signals of CH=N around 8 ppm in their ^{1}H-NMR spectra. The imines are not stable, being easily hydrolyzed and cannot generally be purified by silica gel column chromatography therefore it was used immediately after preparation. In principle, imines can exist in two geometric isomers, namely *E*- and *Z*-isomers (**Figure 3.1**). The *Z*-form is sterically less favourable than the *E*-form because of the repulsion between the R and R′ locating on the same side of the C=N bond.

Figure 3.1 The possible geometric isomers of imines

3.2 Indium mediated allylation of *N*-benzylidenebenzylamine in alcoholic solvents: A back ground

Vilaivan and co-workers[36] has recently discovered that allylation of aldimines can be efficiently performed by allylindium reagent in alcoholic solvents. The reaction of *N*-benzylidenebenzylamine (**I-1**) with the allylindium reagent generated *in situ* by addition of allyl bromide to the suspension of indium powder (Barbier-type conditions) were studied in a variety of solvents (**Table 3.1**). It was found that the best yield and fastest rate of reaction can be realized in alcoholic solvents including isopropanol, methanol and ethanol (**Table 3.1**). While the reaction in water was fast the reaction gave only 1-phenyl-3-buten-1-ol (**III-1**) as the major product (85 %). The structure of product (**III-1**) was confirmed by ^{1}H-NMR, which revealed a triplet signal of the C_1H proton at 5.01 ppm and the complete absence of the *N*-benzyl group signals.

Table 3.1 Indium mediated allylation of *N*-benzylidene benzylamine (**I-1**) in different solvents[a] (Data taken from ref. 36)

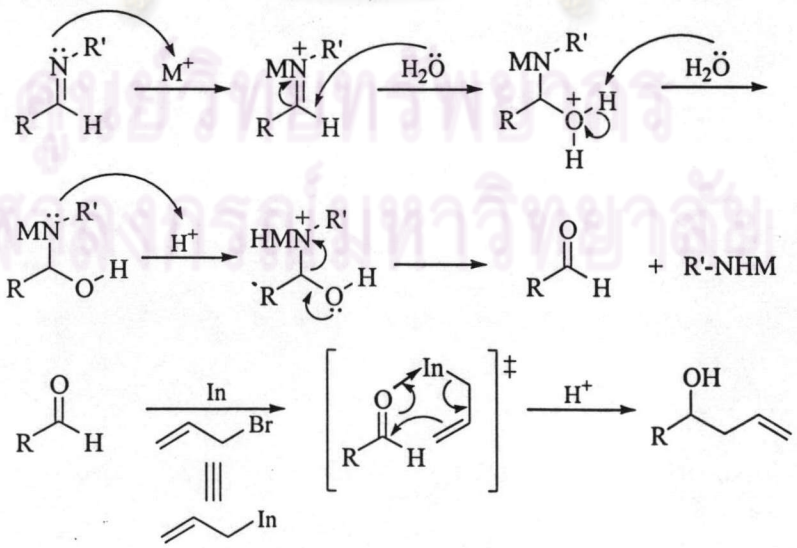


I-1 **II-1** **III-1**

Solvent	Product	Yield (%)[e]
THF	**II-1**	45
^{t}BuOH	[b] –	[b] –
^{i}PrOH	**II-1**	70
MeOH (absolute)[c]	**II-1**	72
EtOH (absolute)[c]	**II-1**	62
H_2O	**III-1**[d]	85

[a] All reactions were performed at 1.0 mmol scale using commercial solvents. No attemps were made to exclude air/moisture.
[b] No reaction
[c] Contains <0.2% water
[d] Only a trace of (**II-1**) was formed
[e] Isolated yield

The formation of the homoallylic alcohol (**III-1**) is presumably the result of allylation of the aldehyde derived from indium salt-catalyzed hydrolysis of the imine (**I-1**) (**Scheme 3.3**).



Scheme 3.3

Vilaivan and co-workers[36] has also noted that trace of water has significant effect to the extent of imine hydrolysis when the reaction was carried out in alcoholic solvents. The yield of the homoallylic amine (**II-1**) dropped from 62 to 7.7 and 3.8 % on changing the solvent from absolute ethanol (< 0.2 % water content) to 95 and 85 % ethanol, respectively. In view of the sensitivity of the reaction to water, it was surprising to obtain reasonably good yields of the desired addition product using commercial absolute alcoholic solvents considering that no attempts to exclude moisture and air were made. The reaction was unique to indium, since treatment of (**I-1**) with zinc powder/allyl bromide or tin powder/allyl bromide in ethanol under the same conditions gave no allylation product and the metal was undissolved.

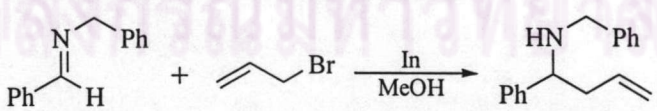
In alcoholic solvents, the rate of indium mediated Barbier-type allylation of aldimines was very fast compare to the allylation in THF. It was proposed that the alcoholic solvents provide a driving force for the forward reaction by protonation of the metal amide intermediate initially formed.[36] However, other explanation are possible such as stabilization of the charged transition state by polar solvents.

This new allylation condition is a significant improvement of traditional methods[15-19, 34] employing anhydrous aprotic solvent and inert atmosphere. It would therefore be interesting to further explore the scope of this reaction.

3.3 Indium mediated allylation of aldimines

3.3.1 The effect of allylation conditions

Table 3.2 Indium mediated allylation of *N*-benzylidene benzylamine (**I-1**) at different ratios of indium powder and allyl bromide



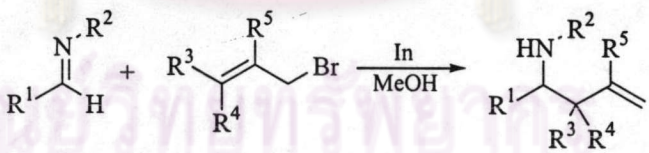
I-1 **II-1**

Entry	In (eq)	Br (eq)	Yield (%)
1	1	1	21
2	1	2	16
3	2	2	51
4	2	3	72
5	2	4	43

The amount and ratio of indium powder and allyl bromides have considerable effects to the yield of the allylation product from indium-mediated allylation of *N*-benzylidene benzylamine (**I-1**) in methanol. Using one equivalent of indium resulted in poor yield regardless of the amount of allyl bromide (entries 1 and 2). Increasing the amount of indium powder to 2 eq gave better yield (entries 3, 4 and 5). The optimum In:allyl bromide ratio appeared to be 2 eq of indium powder and 3 eq of allyl bromide which is consistent with the work by Vilaivan.[36] Therefore we selected this condition for further work.

The reaction has also been attempted in one pot, by stirring benzaldehyde and (*R*)-phenylglycinol in MeOH at room temperature for 30 min to generate imine *in situ* and then adding the indium powder and allyl bromide. The reaction was stirred until the metal had dissolved (20 min). After usual aqueous work-up followed by chromatography, the desired product in was obtained in 64 % yield with considerable amount of alcohol (**III-1**) (36 %). This has proved less efficient compared to the method using pre-formed imines, presumably due to the presence of water formed during the imine formation or incomplete formation of the imine. Although in principle addition of a dehydrating agent might improve the yield, we chose to synthesize the aldimines separately before the allylation.

3.3.2 The effect of substrate structures

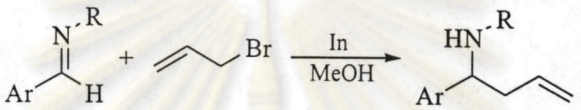


Following the successful results with the *N*-benzylidene benzylamine (**I-1**), the scope of the reaction was explored employing a number of structurally different substituted aldimines and allyl bromides under the same reaction conditions. In all cases, the products were purified by column chromatography after standard aqueous work-up. All compounds were fully characterized by ^{1}H- and ^{13}C-NMR and mass spectrometry.

3.3.2a Variation of type and position of substituents on the aldehyde component

Allylation of the *N*-benzyl and *N*-benzhydryl imines by unsubstituted allyl indium reagent proceeded smoothly to give the expected products in good yield (**Table 3.3**). The presence of potentially reactive substituents such as OH, Cl and Pyridyl at *ortho-*, *meta-* or *para-* position on the aromatic ring of the substrate does not interfere with the reaction. As a result, the reaction showed a high functional group compatibility, demonstrating the versatility of indium reagent.

Table 3.3 Indium mediated allylation of aromatic aldimine (**I-(2-7)**)



I-(2-7) **II-(2-7)**

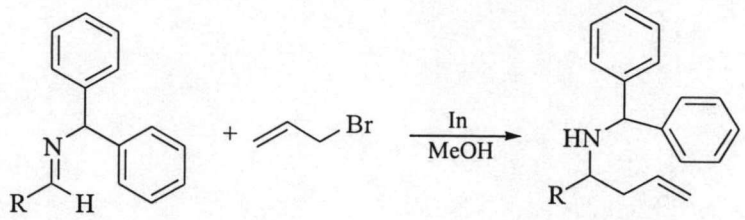
Entry	Substrate	Product	Ar	R	Yield[a] (%)
1	**I-1**	**II-1**	Ph	$PhCH_2$	72
2	**I-2**	**II-2**	3-HOC_6H_4	$PhCH_2$	66
3	**I-3**	**II-3**	4-ClC_6H_4	$PhCH_2$	69
4[b]	**I-4**	**II-4**	4-Pyridyl	$PhCH_2$	50
5[b]	**I-5**	**II-5**	Ph	Ph_2CH	40
6	**I-6**	**II-6**	2-$MeOC_6H_4$	Ph_2CH	72
7	**I-7**	**II-7**	2-Pyridyl	Ph_2CH	79

[a] Products were purified by flash column chromatography
[b] Data from Vilaivan et al.[36]

3.3.2b Addition of allyl indium reagent to aliphatic aldimines

The generality of the reaction was next tested with aldimines derived from enolizable aliphatic aldehydes and benzhydrylamine. The results in **Table 3.4** revealed that a reasonable yield of product can be obtained when R = ^{i}Pr. In spite of a poorer yield was obtained with unbranched, long chain R = $^{n}C_7H_{15}$, the reaction did provide the product. As a result, the scope of the reaction was not limited to imine derived from nonenolizable aldehyde only. The successful allylation of aliphatic imines bearing one or two alpha hydrogens probably reflect the advantage of low basicity of organoindium reagents compared to other traditional organometallic reagents.

Table 3.4 Indium mediated allylation of aliphatic aldimine **I-(8-9)**



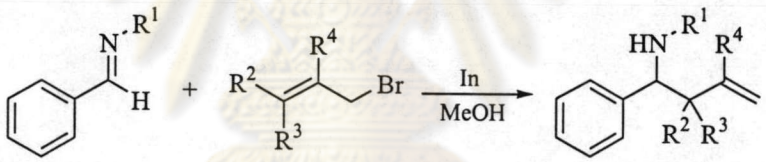
I-(8-9) **II-(8-9)**

Entry	Substrate	Product	R	Yield[a] (%)
1	I-8	II-8	^{i}Pr	61
2	I-9	II-9	$^{n}C_7H_{15}$	20

[a] isolated yield.

3.3.2c The reactions of substituted allyl bromides

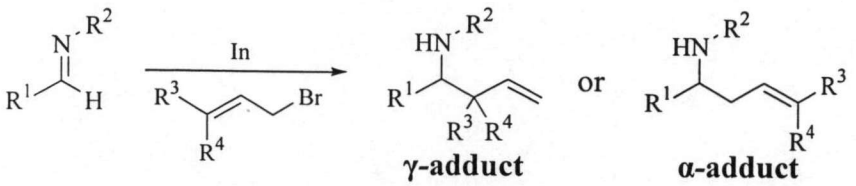
Table 3.5 Indium mediated allylation of substituted allyl bromides



I-(10-13) **II-(10-13)**

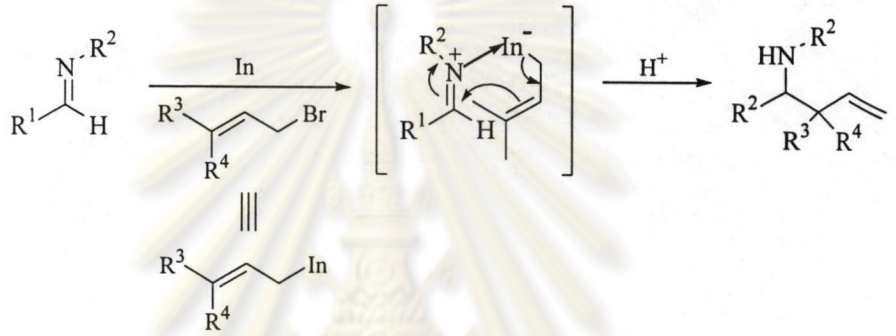
Entry	Substrate	Product	R^1	R^2	R^3	R^4	Yield (%)
1	I-10	II-10	$PhCH_2$	Me	Me	H	19
2	I-11	II-11	Ph_2CH	Me	Me	H	30
3	I-12	II-12	Ph	Me	Me	H	55
4	I-13	II-13	Ph_2CH	Ph	H	H	62

To further explore the scope of this indium-mediated allylation of aldimines, the reaction was performed using substituted allyl bromides. The commercially available 3,3-dimethyl allyl bromide (a γ, γ-disubstituted allyl bromide) and 1-bromo-3-phenyl-2-propene (a γ-monosubstituted allyl bromide) were chosen as substrates. The results were as shown in **Table 3.5**. Generally, the yield was much poorer than unsubstituted allyl bromide. This is not unexpected based on steric consideration. Interestingly, in all cases only the γ-adducts and not the α-adducts have been isolated.



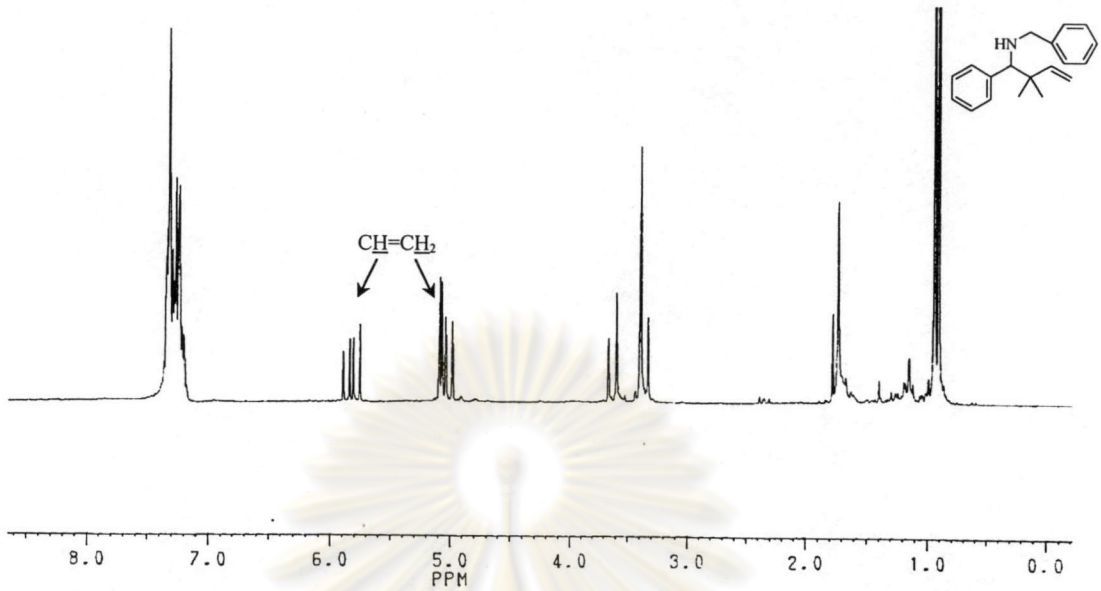
Scheme 3.4

This suggested that allylic rearrangement may take place according to the mechanism shown in **Scheme 3.5**. It is likely that the reaction with unsubstituted allyl bromide would take place *via* the cyclic mechanism in the same way.

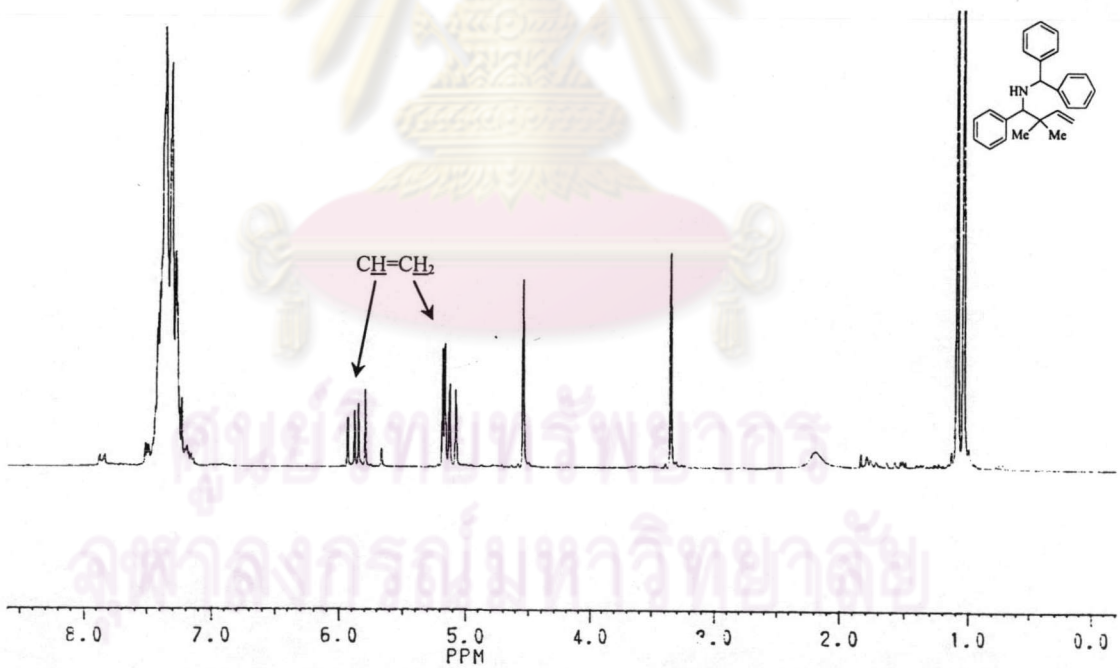


Scheme 3.5

The structure of the products were confirmed by ^{1}H-NMR. *N*-Benzyl-1-phenyl-2,2-dimethylbut-3-enamine (**II-10**) showed two groups of signals of olefinic protons at 5.06 ppm (2H, 2×d) and 5.82 ppm (1H, dd). *N*-diphenylmethyl-1-phenyl-2,2-dimethylbut-3-enamine (**II-11**) and *N*-phenyl-1-phenyl-2,2-dimethylbut-3-enamine (**II-12**) showed similar doublet signals at 5.12/5.85 ppm and 5.22/5.92 ppm respectively. This suggested the presence of terminal alkene group which can only be possible in the *γ*-adducts. For *N*-Diphenylmethyl-1,2-diphenylbut-3-enamine (**II-13**) ^{1}H- and ^{13}C-NMR spectrum of *N*-diphenylmethyl-1,2-diphenylbut-3-enamine (**II-13**) further revealed that the compound consisted of 2 isomers, the *syn*- and *anti*-isomers, in the ratio of 80:20. The major isomer showed a triplet signal of C<u>H</u>CH=CH_2 at 3.71 and two doublet signals of CH=C<u>H</u>$_2$ at 4.95 ppm and multiplets of C<u>H</u>=CH_2 at 5.85 ppm. From the limited data available it was not possible to tell the configuration of major product whether it is *syn*- or *anti*- isomer.

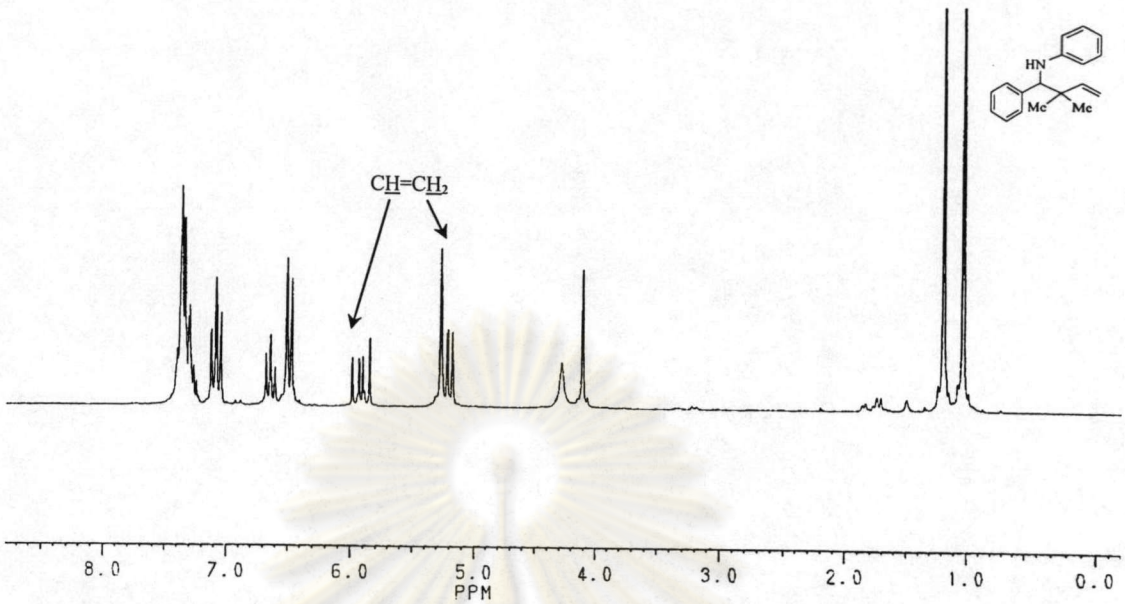


a) *N*-benzyl-1-phenyl-2,2-dimethylbut-3-enamine (**II-10**)

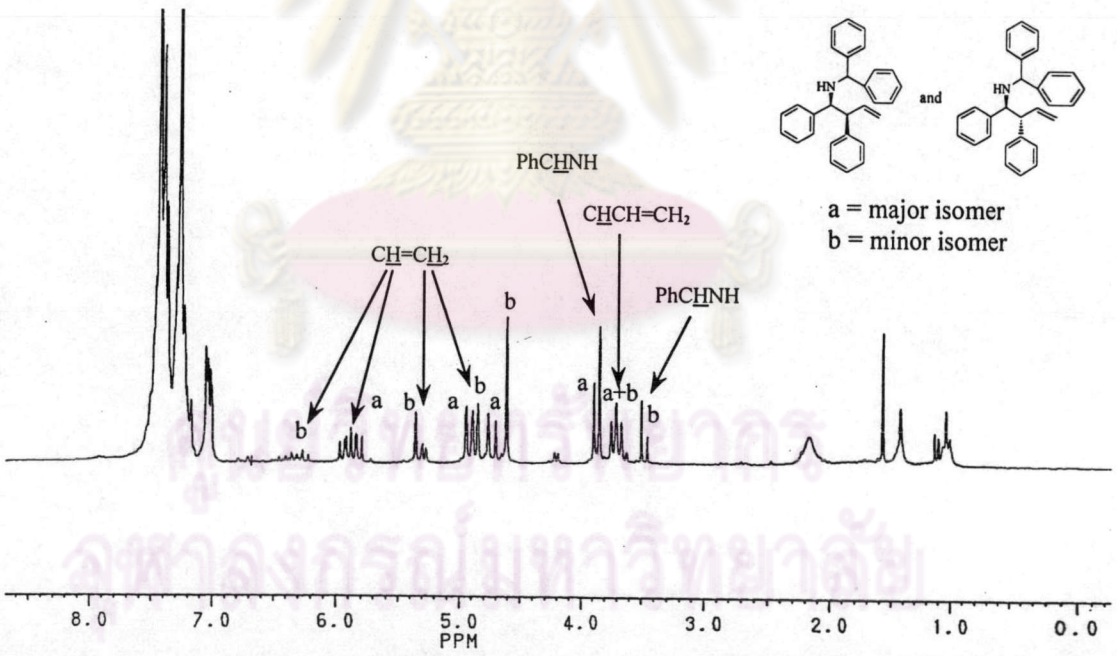


b) *N*-diphenylmethyl-1-phenyl-2,2-dimethylbut-3-enamine (**II-11**)

Figure 3.2 The ^{1}H-NMR spectrum of the reaction products of aldimine with substituted allyl bromides/ Indium powder



(c) *N*-phenyl-1-phenyl-2,2-dimethylbut-3-enamine (**II-12**)



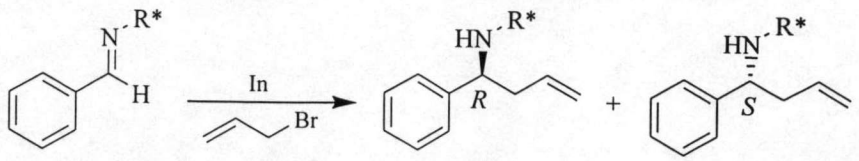
(d) *N*-diphenylmethyl-1,2-diphenylbut-3-enamine (**II-13**)

Figure 3.2 The ^{1}H-NMR spectrum of the reaction products of aldimine with substituted allyl bromides/Indium powder (Continued)

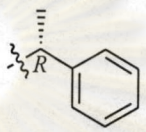
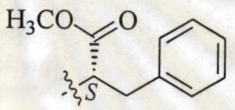
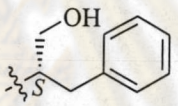
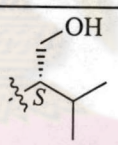
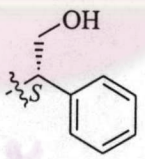
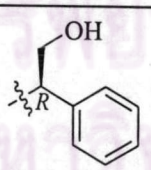
3.4 The investigation of chiral amines as auxiliaries for asymmetric allylation of aldimines

It is evidenced that by using chiral aldimines derived from chiral amines, asymmetric addition should be possible. Vilaivan[36] has previously discovered that (*R*)-phenylglycinol is a good chiral auxiliary for such addition (*ds* > 9:1) while (*R*)-phenylethylamine gave a much poorer result (*ds* < 7:3). In order to find the best chiral auxiliary, the allylation of chiral aldimines **I-(14-18)** derived from benzaldehyde and appropriate chiral amines were chosen as model reactions. The allylation reaction was carried out in the presence of 2 eq of indium powder and 3 eq of allyl bromide in absolute ethanol or methanol at room temperature as described earlier. (*R*)-Methylbenzylamine, as well as (*S*)-phenylalanine methyl ester and (*S*)-phenylalaninol gave poor diastereoselectivity (**Table 3.6**). The more bulky isopropyl group together with the ability to chelate the metal of (*S*)-valinol make it a better auxiliary.[33] This auxiliary has previously shown to be very effective in Pd^0-catalyzed allylation of aldimine.[30] Among all chiral amines investigated, (*R*)-phenylglycinol was found to give the most impressive results whereby the desired allylation products were isolated in 89 % yield virtually as a single diastereoisomer as shown by ^1H- and ^{13}C-NMR spectroscopy (at 500 and 125 MHz respectively). The optical rotation of the product **II-14** derived from (*R*)-phenylglycinol is –35.2 (*c* = 1.05, $CHCl_3$) which is in accordance with literature[30] ($[\alpha]_D^{29}$ = -42.3, *c* = 4.00, $CHCl_3$). Based on the optical rotation, the configuration of the newly formed stereogenic center is proposed to be *R* (to be confirmed later). The corresponding reaction employing the also readily available (*S*)-phenylglycinol gave the product with opposite configuration at the new stereogenic center formed as shown by the optical rotation ($[\alpha]_D^{24}$ = +34.6, *c* = 1.01, $CHCl_3$).

Table 3.6 Addition of allyl indium reagent to chiral aldimines



I **(*R*)-II** **(*S*)-II**

Entry	Substrate	Product	R*	%Yield	*ds* (major:minor isomer)[b]
1[a]	**I-14**	**(*R*)-II-14, (*S*)-II-14**		76	70:30
2	**I-15**	**(*R*)-II-15, (*S*)-II-15**		55	73:27
3	**I-16**	**(*R*)-II-16, (*S*)-II-16**		40	77:23
4	**I-17**	**(*R*)-II-17, (*S*)-II-17**		51	90:10
5	**I-18**	**(*R*)-II-18, (*S*)-II-18**		86	>99:1
6	**I-19**	**(*R*)-II-19, (*S*)-II-19**		89	>99:1

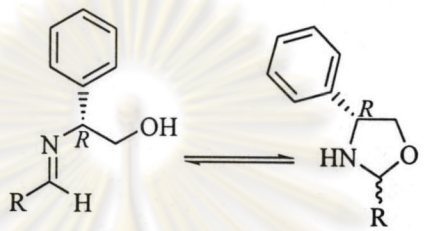
[a] Data from Vilaivan et al.[36]
[b] Determined by ^{1}H-NMR

From **Table 3.6**, it is evidenced that the chiral auxiliary possessing a donor atom capable of chelation (together with the imine nitrogen) is necessary for high diastereoselectivity. In addition, the R-group must be sufficiently bulky, thus phenyl (entries 5, 6) and isopropyl (entry 4) are much better than benzyl group (entries 2, 3). Since, (*S*)- and (*R*)-phenylglycinol auxiliary gave the desired product in high yield

and diastereomeric ratio, therefore they were chosen as chiral auxiliary for further studies, especially the less expensive (*R*)-isomer.

3.5 Addition of allyl indium reagent to chiral aldimines derived from aldehydes and (*R*)-phenylglycinol

The aldimines used in this study were prepared from (*R*)-phenylglycinol and aldehydes described in section **3.1**



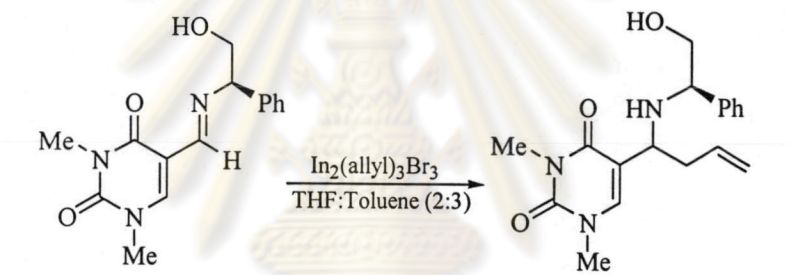
I-a **I-b**

Scheme 3.6

The chiral imine **I-a** were obtained quantitatively by mixing (*R*)-phenylglycinol with the corresponding aldehyde in the presence of anhydrous magnesium sulfate in dichloromethane at room temperature overnight. The structure of products were established by ^{1}H-NMR. Interestingly, imines derived from aromatic aldehydes existed in equilibrium with the tautomeric oxazolidine diastereomers **I-b** as indicated by the presence of oxazolidine C-H signals at 4.26 ppm. The content of the oxazolidine increases with more electrophilic aldehydes. For imines derived from aliphatic aldehydes, the oxazolidine is the major tautomer and no CH=N signal was observed.

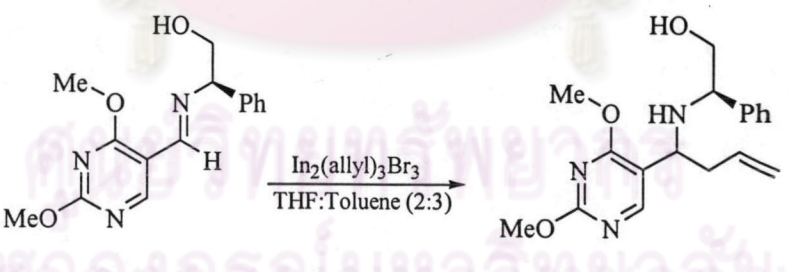
The generality of the asymmetric allylation reaction employing (*R*)-phenylglycinol as chiral auxiliary was tested with a variety of aldimines derived from substituted aromatic and aliphatic aldehydes (**Tables 3.7, 3.8**). This reaction is applicable to a wide range of substrates to give the products in fair to good yields and excellent diastereoselectivity. For substrates bearing *para*-substituted benzene (entries 1, 10, 11) the diastereoselectivity is approaching 100 % as no sign of the other diastereomer was observed according to ^{1}H- and ^{13}C-NMR analysis. Imines bearing *ortho*- and *meta*-substitution (entries 4, 5, 7-9) gave somewhat poorer as indicated by ^{1}H- and ^{13}C-NMR.

It is interesting to observe that the imines derived from salicylaldehyde (entry 6) and heteroaromatic aldehydes (entry 2, 3) bearing substituents capable of coordinating ability at the *ortho*-position gave excellent diastereoselectivity. Kumar[34] and co-workers has recently reported an indium-mediated allylation of the Schiff bases derived from uracils and chiral amino alcohol in THF/toluene. They suggested that complexation of the C-4 carbonyl oxygen of the uracil moiety with indium is essential to obtain diastereoselectivity (*ds* > 98:2) since the corresponding imines derived from 2,4-dimethoxy-5-formylpyrimidine gave virtually no diastereoselectivity (**Scheme 3.7**). The reason for poor selectivity observed for *meta*-substituted aromatics (entries 7-9) is less clear. However, from the present study, it is evidenced that the presence of *ortho*- chelating moiety on the aldehyde is not essential to give high diastereoselectivity as suggested by Kumar[34].



I-20a **II-20a**

(62 %, *ds* = >98:2)

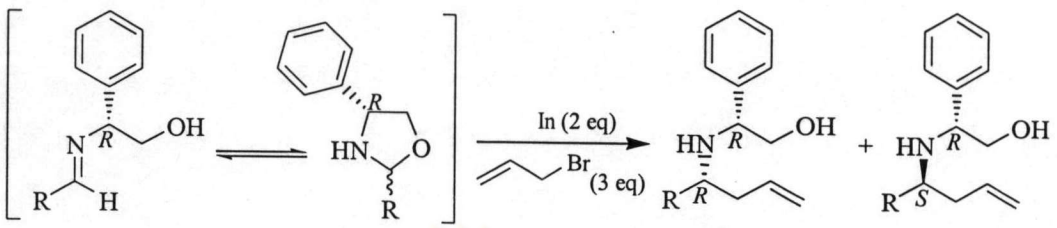


I-20b **II-20b**

(66 %, *ds* = 50:50)

Scheme 3.7

Table 3.7 Addition of allylindium reagent to chiral aldimines derived from aromatic aldehydes and (*R*)-phenylglycinol



I **(*R,R*)-II** **(*R,S*)-II**

Entry	Substrate	Major Product	R	Yield (%)	$[\alpha]_D^{24}$, $CHCl_3$	*ds*[a] (major : minor)
1	**I-19**	**(*R,R*)-II-19**	Ph-	89	-31.4 (*c*=1.01)	>99:1[b]
2	**I-21**	**(*R,R*)-II-21**	2-Pyridyl-	98	-15.2 (*c*=0.99)	>99:1[b]
3	**I-22**	**(*R,R*)-II-23**	2-Furyl	79	-5.7 (*c*=1.05)	>99:1[b]
4	**I-23**	**(*R,R*)-II-23**	2-ClC_6H_4-	94	-36.2 (*c*=1.02)	94:6
5	**I-24**	**(*R,R*)-II-24**	2-$MeOC_6H_4$-	82	-45.2 (*c*=1.04)	80:20
6	**I-25**	**(*R,R*)-II-25**	2-HOC_6H_4-	49	-63.6(*c*=0.89)	>99:1[b]
7	**I-26**	**(*R,R*)-II-26**	3-ClC_6H_4-	71	-22.1 (*c* = 1.13)	94:6
8	**I-27**	**(*R,R*)-II-27**	3-$MeOC_6H_4$-	51	-45.2 (*c* = 1.04)	95:5
9	**I-28**	**(*R,R*)-II-28**	3-HOC_6H_4-	78	-36.1 (*c*=0.97)	94:6
10	**I-29**	**(*R,R*)-II-29**	4-ClC_6H_4-	91	-18.3 (*c*=1.04)	>99:1[b]
11	**I-30**	**(*R,R*)-II-30**	4-MeC_6H_4-	98	-24.4 (*c*=1.20)	>99:1[b]

[a] determined by ^{1}H-NMR.
[b] Only one diastereomer was observed by 200 and 500 MHz ^{1}H-NMR and 50 MHz ^{13}C-NMR analysis.

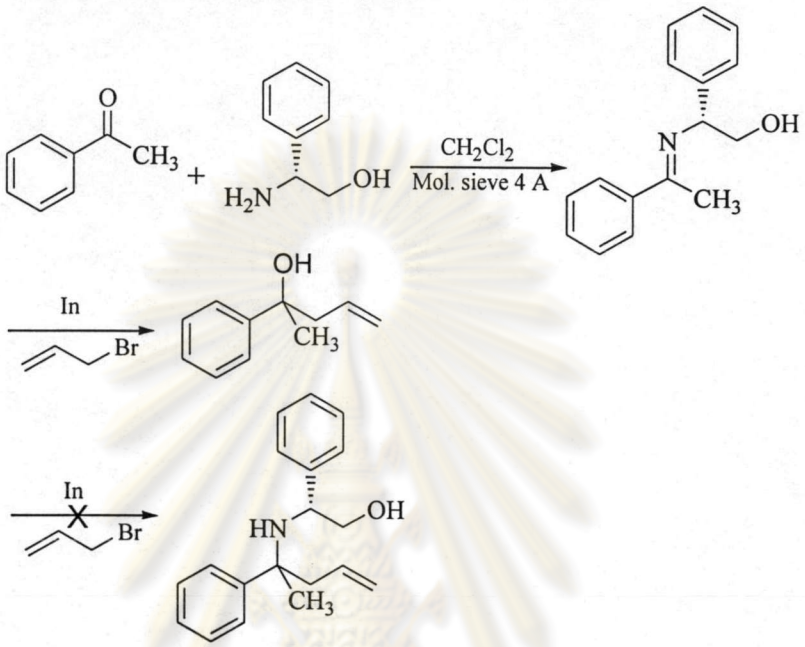
The reactions with imines derived from aliphatic aldehydes also gave the desired products in fair to good yield. In all cases the diastereoselectivity was excellent.

Table 3.8 Addition of allylindium reagent to chiral aldimines derived from aliphatic aldehydes and (*R*)-phenylglycinol

R	Substrate	Product	Yield (%)	$[\alpha]_D^{24}$, $CHCl_3$	*ds* (major : minor)
i-Propyl-	**I-31**	**(*R,R*)-II-31**	100	-122.9 (*c*=0.98)	>99:1
n-Propyl-	**I-32**	**(*R,R*)-II-32**	51	-91.4 (*c*=1.51)	>99:1
n-Butyl-	**I-33**	**(*R,R*)-II-33**	33	-73.8 (*c*=0.66)	>99:1
Cyclohexyl-	**I-34**	**(*R,R*)-II-34**	78	-78.9 (*c*=1.07)	>99:1
Cinnamyl-	**I-35**	**(*R,R*)-II-35**	87	+28.7 (*c*=1.03)	>99:1

3.6 Addition of allylindium reagent to chiral ketimines derived from ketones and (*R*)-phenylglycinol

To test whether the allylation condition is applicable to ketimines, an imine derived from acetophenone and (*R*)-phenylglycinol was made.

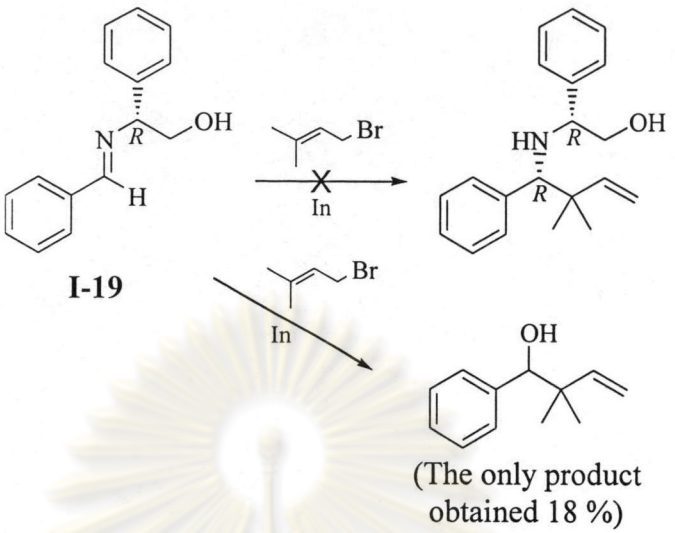


Scheme 3.8

Disappointingly, the allylation gave rise to a mixture of phenylglycinol and 1,2,2-trimethyl-phenylbut-3-en-1-ol resulting from allylation of acetophenone as shown by ^{1}H-NMR (**Scheme 3.8**). Therefore, it is concluded that the present condition of indium mediated allylation is not applicable to ketimines.

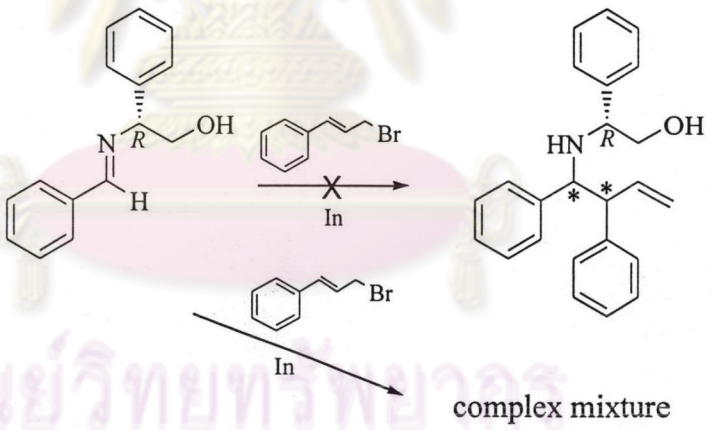
3.7 Additon of allylindium reagent to chiral aldimines by using substituted allyl bromides

The scope of indium-mediated allylation of aldimines was further tested by performing the reaction, using substituted allyl bromides. For the allylation of aldimine **I-19** derived from (*R*)-phenylglycinol and benzaldehyde with 3,3-dimethylallyl bromide, the only isolable product is the 2,2-dimethyl-1-phenylbut-3-en-1-ol (18 %) (**Scheme 3.9**).



Scheme 3.9

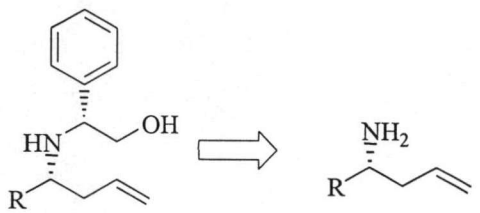
For the corresponding allylation with 3-bromo-1-phenyl-1-propene, the reaction gave rise to complex mixture shown by ^{1}H-NMR (**Scheme 3.10**).



Scheme 3.10

From the results shown above, it is concluded that only unsubstituted allyl bromide is effective in this reaction condition somewhat which might restrict the application of the reaction. Nevertheless, the broad substrate tolerance and high diastereoselectivity together with its simplicity make this reaction potentially useful.

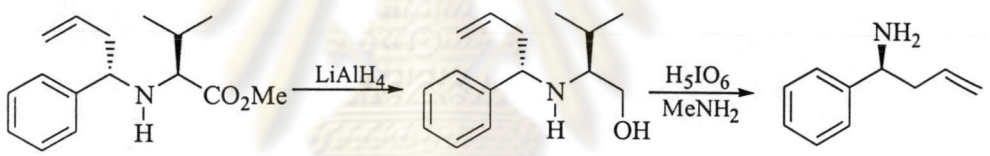
3.8 The removal of chiral auxiliary



II **V**

Chiral homoallylamines are valuable synthons for the preparation of biologically active components. However, an effective method to remove the chiral auxiliary must be available so as to utilize the full potential of this reaction. Several literature methods have been attempted as will be discussed in details below.

3.8.1 The oxidative cleavage with periodic acid in the presence of methylamine

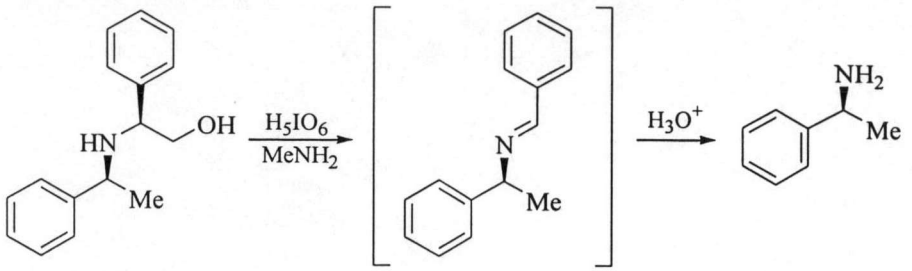


II-36 **II-37** **V-1**

Scheme 3.11

Umani-Ronchi[21] and Savoia[25] reported the synthesis of (*S*)-1-phenyl-3-butenamine (**V-1**) from the allylation product of imines derived from (*S*)-valine methyl esters and aldehydes by a two-step sequence. The first step is the reduction of the methyl ester with $LiAlH_4$ followed by subsequent oxidative cleavage with H_5IO_6 in the presence of excess $MeNH_2$ (**Scheme 3.11**). The homoallylic amine was obtained optically pure in 86 % overall yield.

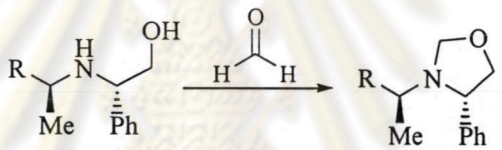
Furthermore, Coates[38] reported that the similar oxidative cleavage of the optically active 2-phenyl-2-(1′-phenylethylamino)-ethanol (**VI**) gave (*S*)-phenethylamine (**V-2**) in 70 % yield and 94 % *ee*.



VI **VII-1** **V-2**

Scheme 3.12

Coates[38] have found that methylamine is required additive in this cleavage reaction. In the absence of methylamine, formaldehyde resulted from the initial oxidative cleavage of amino alcohol auxiliary reacted competitively with (**VIII**) to give oxazolidine adducts (**IX**) as a major product (oxazolidine/imine ratio ~ 2:1) which was stable to the cleavage condition.



VIII **IX**

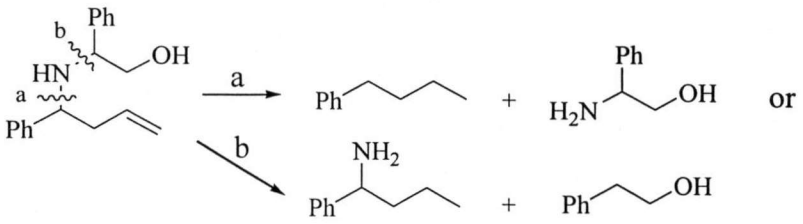
Scheme 3.13

Our attempts to repeat the reaction under this condition failed as shown by ^{1}H-NMR of the crude reaction products. The reasons are not quite clear, but this may be attributed partly to the old sample of H_5IO_6 used.

3.8.2 The hydrogenolysis in the presence of acid

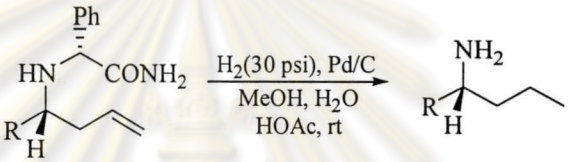
The phenylglycinol auxiliary, being a benzylic amine, can be removed by hydrogenolysis.[39] Three major drawbacks of this method include:

1) The harsh condition required for hydrogenolysis of benzylic amines. (*e.g.* high pressure, temperature and requirement of additives such as HOAc[40])
2) Incompatibility with the allyl group (the double bond is easily hydrogenated).
3) The reaction is applicable only when R ≠ aryl since otherwise ambiguous hydrogenolysis may result *e.g.* (**Scheme 3.14**).



Scheme 3.14

Recently, the addition of allylzinc bromide to imines derived from (*R*)-phenylglycine amide as chiral auxiliary is reported (**Scheme 3.15**).[23] Removal of the auxiliary by hydrogenation lead to the saturated amines, also in high enantiomeric purity.[23]

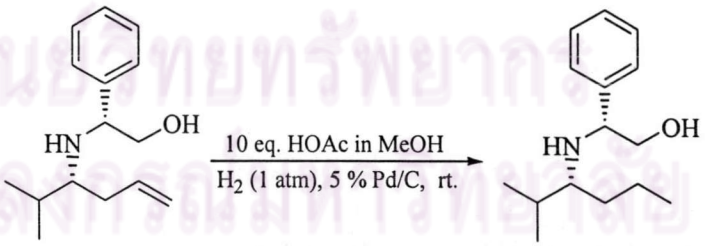


II-38 **V-3**

R= Ph, ^{i}Pr (49-64 % yield, 97 % *ee*)

Scheme 3.15

In our hands, the removal of the chiral auxiliary by hydrogenation leads to the loss of the allylic functionality as determined by the ^{1}H-NMR of the product, although no auxiliary cleavage was observed.

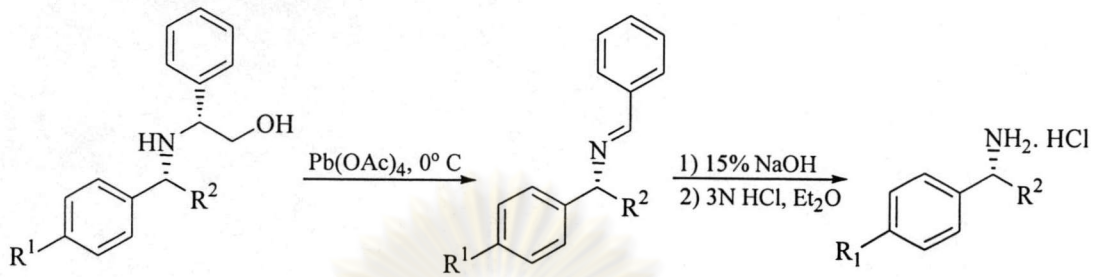


Scheme 3.16

Our attempts to repeat the reaction under a variety of conditions (hydrogen donor: H_2, HCO_2NH_4; catalyst: 10 % Pd-C, $Pd(OAc)_2$, $Pd(OH)_2$-C; additive: none, HOAc) gave no cleavage product, only saturation of the allyl group was observed as shown by the disappearance of the olefinic proton signal in ^{1}H-NMR spectra of the products.

3.8.3 Oxidative removal of the chiral auxiliary with lead tetraacetate

a) Literature review



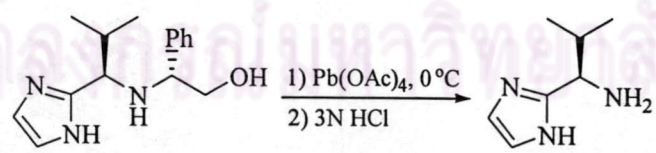
II-39 **VII-2** **V-4**

R^1 = H, Br, OMe; R^2 = CH_3, C_2H_5, CH_2Ph

Scheme 3.17

Wu and Pridgen[26] have reported that oxidative cleavage of the aminoalcohol with lead tetraacetate is more effective than hydrogenolysis in removal of phenylglycinol auxiliary and is fully compatible with the allyl group. The procedure involves stirring the substrate with $Pb(OAc)_4$ in CH_2Cl_2 : MeOH (2:1) at 0 °C for a few minutes followed by addition of 15 % aqueous NaOH to quench the reaction. The crude imine obtained was then deprotected by stirring with 3 N HCl/ether (46-65 % yield, 92-99 % *ee*) (**Scheme 3.17**).

Pridgen and co-workers[45] have reported a synthesis of 2-(1′-amino-2′-methylpropyl) imidazole (**V-5**), a key synthon in the synthesis of SB 203386 potent protease inhibitor, by this approach.



II-40 **V-5**

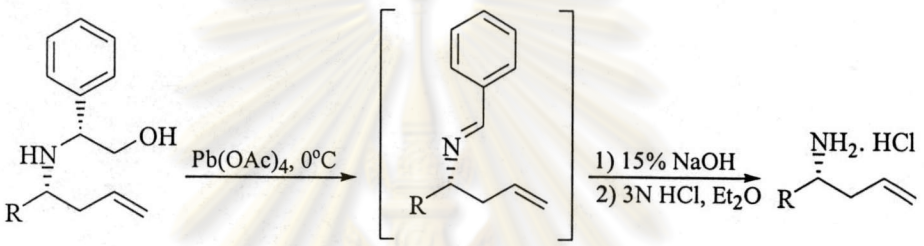
Scheme 3.18

Moreover, the method for synthesis of nonracemic amines has been reported by Pridgen[45] wherein organometallic nucleophiles were added to nonracemic oxazolidines which in turn were prepared by condensation of the appropriate aldehyde

with optically active phenylglycinol. Oxidative removal of the chiral auxiliary yielded nonracemic primary amines. Compound **II-40** was converted to (*R*)-**V-5** in 86 % yield and > 99 % *ee* on treatment with lead tetraacetate.

b) The removal of the chiral auxiliary with lead tetraacetate under conventional protocol

We decided to follow the well-documented oxidative procedure to cleave the 2-phenylethanol moiety from (2*R*)-2-phenyl-2-[(1′*R*)-1′-phenylbut-3′-enylamino] ethanol (**II-19**) by using lead tetraacetate.



II-(19,31) **VII-(3,4)** **V-(6,7)**

R = Phenyl (**II-19, VII-3, V-6**), isopropyl (**II-31, VII-4, V-7**)

Scheme 3.19

Treatment of (2*R*)-2-phenyl-2-[(1′*R*)-1′-phenylbut-3′-enylamino]ethanol (**II-19**) with $Pb(OAc)_4$ in CH_2Cl_2: MeOH (2:1) at 0 °C for 1 hour gave *N*-benzylidine-(1-phenylbut-3-ene-1-amine) (**VII-3**) as shown by ^{1}H-NMR. Hydrolysis of this intermediate using 3N HCl / Et_2O overnight gave the desired deprotection product 1-phenyl-but-3-ene-1-amine (**V-6**) as hydrochloride salt after evaporation of the aqueous phase. Unfortunately, the yield was rather poor (18 % of desired product), and more seriously, a significant level of racemization (30 %) was observed after derivation with Boc-(*R*)-phenylglycine and Boc-(*S*)-phenylglycine.[42] The (*R*) isomer was found to be the major product (see section 3.9.3). Since the derivatization step has been proven to be racemization-free, the only possible step that racemization can occur is the auxiliary cleavage step.

Deprotection of the amine (**II-31**) (R = ^{i}Pr) derived from aliphatic aldehydes resulted in the desired product in only 18 % yield with 20 % racemization.

It was previously shown that imine of the type (**VII-5**) is subjected to aza-Cope rearrangement as follows:[23] The reaction may fake place spontaneously under thermal conditions. However, in our case the intermediate imine does not seem to rearrange before acid-treatment therefore the rearrangement is probably acid-catalyzed.

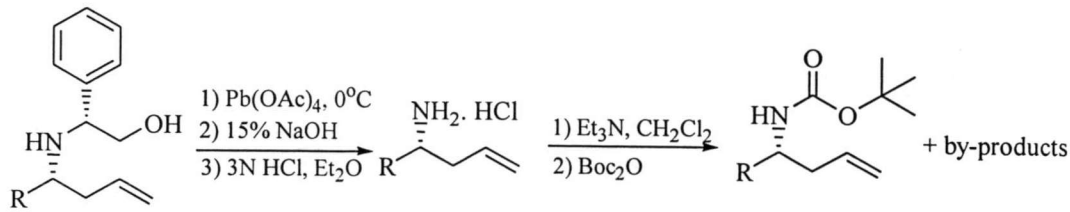
VII-5 **I-36**

Scheme 3.20

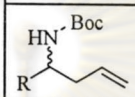
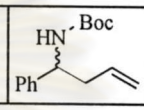
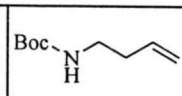
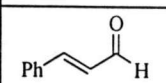
We suspected that such mechanism is responsible for the racemization and also lead to low yield due to the formation of by-product. We have confirmed that this is the case by identifying all the products form such cleavage reaction as follows:

The cleavage products, which are derived from the oxidative removal of the chiral auxiliary from amines **II-19** R = Ph, **II-24** R = 2-OMeC$_6$H$_4$, **II-31** R = ^{i}Pr and **II-35** R = Cinnamyl with lead tetraacetate, followed by hydrolysis could not be separated by flash column chromatography due to their highly polar nature. Therefore, the amine products were first protected by *tert*-butoxycarbonyl group by treatment with Boc_2O/Et_3N. The cleavage product and aza-Cope rearrangement by-products were purified by flash column chromatography and identified by ^{1}H-NMR (**Table 3.9**).

Table 3.9 The oxidative removal of the chiral auxiliary with lead tetraacetate and the aza-Cope rearrangement by-products (isolated as *N*-Boc derivatives)



II **V** **X**

Entry	Substrate	R	Yield (%)			
						**Others**
1	**II-19**	Ph	63[a]		37[b]	-
2	**II-24**	2-MeOC$_6$H$_4$	56[b]	12[b]	8[b]	-
3	**II-31**	^{i}Pr	27[c]	15[a]	3[b]	-
4	**II-35**	Cinnamyl	67[b]	18[b]	4[b]	

[a] Isolated yield, 30 % racemization
[b] Calculated yield from ^{1}H-NMR
[c] Isolated yield, 20 % racemization

In all reactions *N-tert*-butoxycarbonyl-(*R*)-1-phenyl-but-3-enamine and *N-tert*-butoxycarbonyl-1-but-3-enamine were found to be common by-products. When R = Ph (entry 1) product and (degenerate) by-product, *N-tert*-butoxycarbonyl-1-phenyl-but-3-enamine were inseparable mixture of enantiomers. Furthermore, in the case of R = cinnamyl, cinnamaldehyde was also detected by ^{1}H-NMR spectrum as evidenced by the presence of a doublet CHO signal at 9.77 ppm.

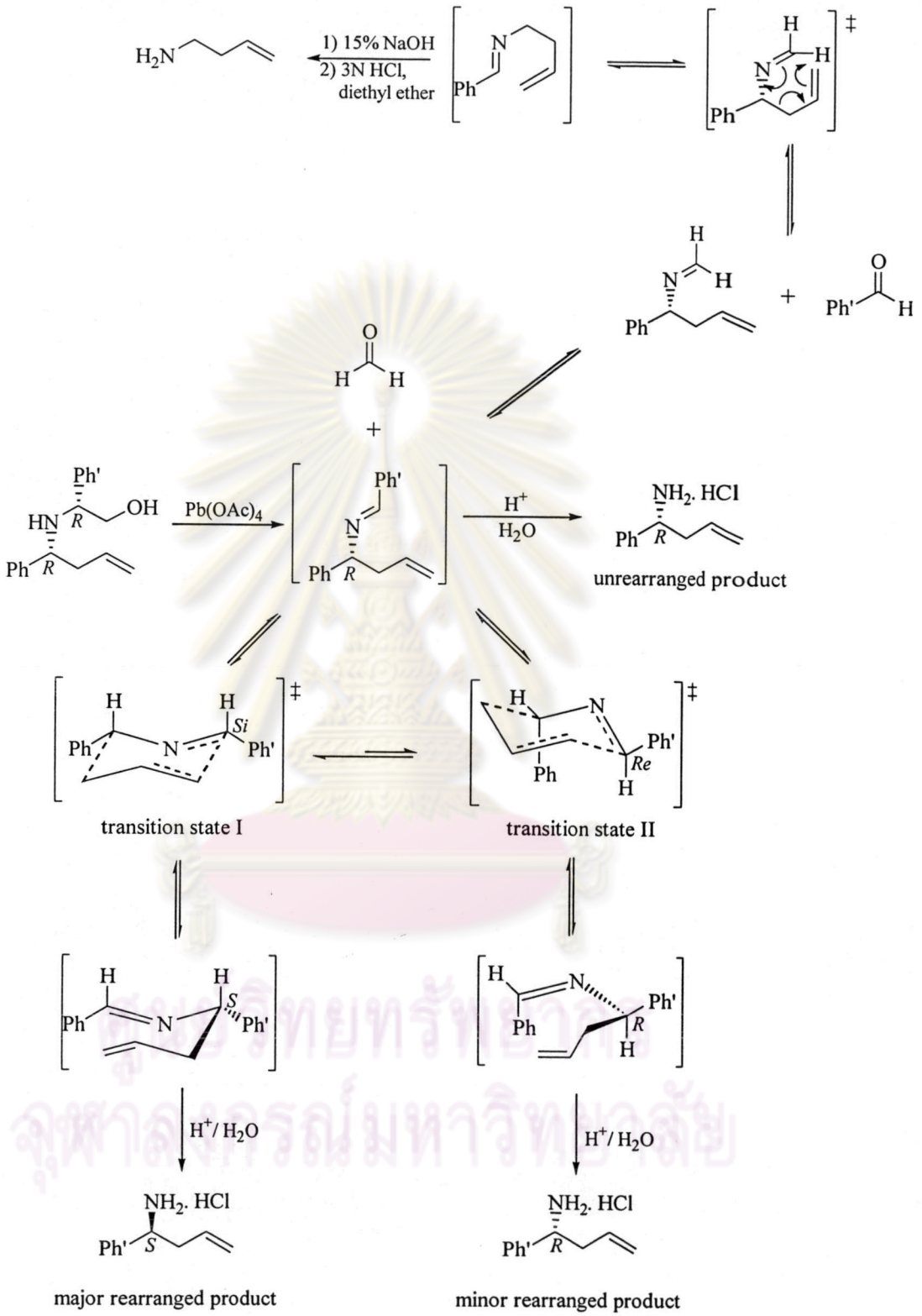
We would like to propose an explanation for the above observation of racemization and formation of by-products as follows:

In the simplest case, R = Ph, the aza-Cope rearrangement would be degenerate, *ie*, the starting material and the product are the same. However, this is not strictly true if we consider the configuration of the products. Let's suppose R = Ph and configuration of the starting imine is *R*. The aza-Cope rearrangement should proceed through one of the two chair-like transition state models shown in **Scheme 3.21**. The one possessing transition state I has both Ph groups occupying

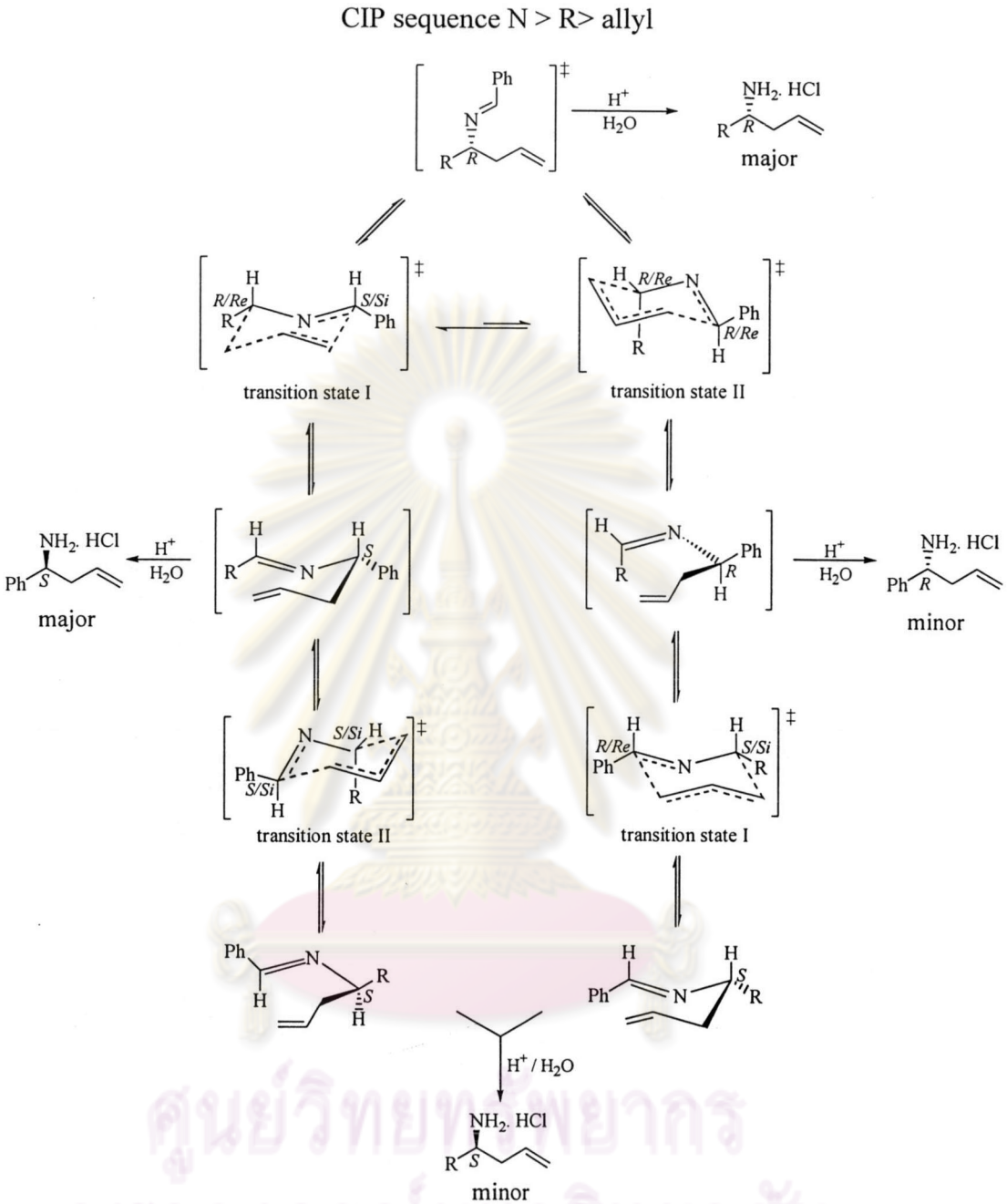
equatorial positions while the transition state II has one Ph group in an axial position. As evidenced from **Scheme 3.21**, the transition state I would result in the same compound as the starting material, but with the opposite (*S*)-configuration. Since the process can repeat again and again, racemization is expected.

For R ≠ Ph, the situation would be more complicated, but the result would also lead to racemization (**Scheme 3.22**). Assuming the six-membered cyclic transition state model, the transition state I should lead to the by-product (R = Ph) with *opposite* configuration to the starting homoallylic imine (R = ^{i}Pr). On the other hand, the reaction can also proceed *via* a transition state II pathway whereby one R group occupying axial and the other occupying equatorial positions to give the product with the same configuration which, upon another aza-Cope rearrangement would result in racemization. Although the latter pathway is expected to be the minor one, its occurrence might not be negligible. Analysis of the configuration of the isolated by-product (R = Ph) by optical rotation measurement and by derivatizing with Boc-(*R*)-phenylglycine nicely confirmed that it is indeed a mixture of both enantiomers with the (*S*)-enantiomer being predominate (*S*:*R* = 80:20). It is therefore conceivable that successive aza-Cope rearrangement of these intermediates would results in decreased enantiomeric purity of all products involved as observed experimentally (**Scheme 3.22**).

When the intermediate imine (**VII-4**) was isolated free from formaldehyde by-product, the rearrangement and racemization could still take place upon treatment with acid. This suggests that the racemization does not require the presence of formaldehyde.


1) 15% NaOH
2) 3N HCl,
diethyl ether
Pb(OAc)4
H+
H2O
NH2. HCl
unrearranged product
transition state I
transition state II
H+/ H2O
H+/ H2O
NH2. HCl
NH2. HCl
major rearranged product
minor rearranged product

Scheme 3.21



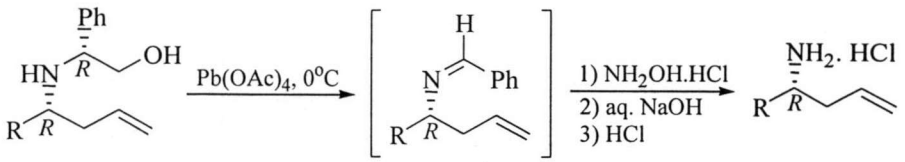
Scheme 3.22

We have tried every possible way to solve the problem of aza-Cope rearrangement using various alternative cleavage methods such as aq NaOBr, NaOCl, PBr_3 followed by DBU treatment, but none of these was as effective as $Pb(OAc)_4$ oxidation. As a result, our attempt was focused on finding the most effective method for hydrolysis of the imine intermediate. The details of which will be discussed in the next section.

c) Racemization-free removal of the chiral auxiliary with lead tetraacetate

Broxterman[23] reported an effective routes for cleavage of the imines obtained from a different method using hydroxylamine hydrochloride. We have applied this method to cleavage the imine derived from $Pb(OAc)_4$ oxidation of the aminoalcohol such as *N*-benzylidene-(1-phenylbut-3-ene-1-amine) (**VII-3**) and *N*-benzylidene-(1-isopropyl-but-3-ene-1-amine) (**VII-4**). The oxidation product, without isolation, was treated with large excess (10 eq.) of hydroxylamine hydrochloride in MeOH:CH_2Cl_2 (1:1) at 0 °C until all the starting material was consumed (TLC). The mixture was then treated with 10 % HCl until pH=1 and was extracted with diethyl ether to remove non-basic impurities. The water phase was adjusted to pH = 12 with 15 % NaOH and was re-extracted with diethyl ether. The ether phase was stirred with excess of methanolic HCl (generated *in situ* from acetyl chloride and MeOH). The solvent was evaporated furnishing the homoallylic amine as a hydrochloride salt. In this way, no by-products derived from aza-Cope rearrangement was observed in the crude product. Furthermore, the chiral integrity of the products in all case were secured as confirmed by derivatization with Boc-D-phenylglycine and Boc-L-phenylglycine (section **3.9**), which showed only one compound in each case. Therefore, $Pb(OAc)_4$ oxidation followed by treatment with hydroxylamine hydrochloride is the method of choice for racemization-free deprotection of the phenylglycinol moiety from homoallylic amine. The mechanism of imine cleavage by NH_2OH can be written as follows (**Scheme 3.23**). The rate of NH_2OH is probably to cleave the imine as well as to trap the aldehyde by-product so that the reversible imine formation is not possible. The high mucleophilicity of $NH_2OH{\cdot}HCl$ as well as the lower acidity as compared to 3N HCl ensure minimum life time of the imine and its conjugate acid therefore reducing the chance of aza-Cope rearrangement.

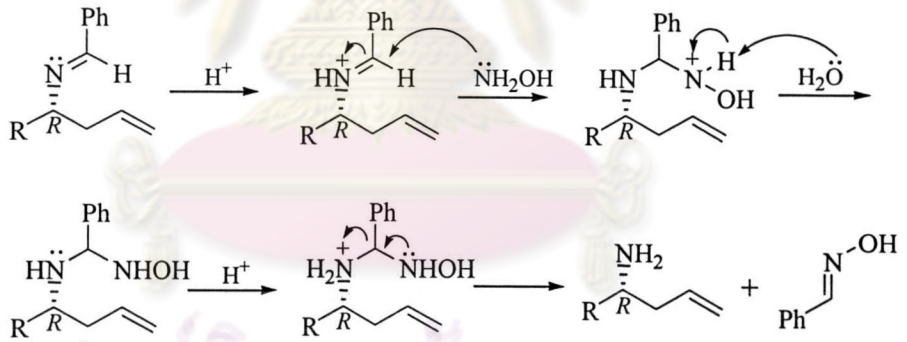
Table 3.10 Removal of the auxiliary from the homoallylic amines



II **VII** **V**

Entry	Substrate	Product	R	Yield (%)	$[\alpha]_D^{24}$, $CHCl_3$	*R*:*S*[a]
1	**II-19**	**V-6**	Ph	78	-1.2 (*c*=0.85)	> 99:1
2	**II-21**	**V-10**	2-Pyridyl	74	+20.3 (*c*=1.02)	> 99:1
3	**II-24**	**V-8**	2-$MeOC_6H_4$	82	-6.9 (*c*=1.04)	80:20[b]
4	**II-31**	**V-7**	^{i}Pr	74	-4.8 (*c*=0.83)	> 99:1
5	**II-32**	**V-11**	^{n}Pr	82	-94.2 (*c*=1.35)	> 99:1[c]
6	**II-34**	**V-12**	^{c}Hex	56	-0.71 (*c*=0.98)	> 99:1
7	**II-35**	**V-9**	Cinnamyl	73	+23.1 (*c*=0.78)	> 99:1

[a] Determined from 200 MHz ^{1}H-NMR spectra of the product after derivatization with (*R*)- and (*S*)-Boc-phenylglycine; [b] The starting material was a 80:20 mixture of *RR*:*RS* diastereomers; [c] The absolute configuration of the major product must be assigned as *S*. In fact the absolute configuration is the same as other compounds, but the lower priority of R group as compared to allyl group according to the CIP sequence rule makes the stereochemical designation *S* rather than *R*.



Scheme 3.23

3.9 The assignment of the absolute configuration of the homoallylic amines

3.9.1 General principle

There are a number of methods to assign the absolute configuration of chiral molecules. One characteristic of chiral molecules is that the separated enantiomers cause the plane of polarized light to rotate by opposite but equal amounts. The absolute configuration of new chiral compounds can be determined by compare the sign of rotation with compounds of known configuration under similar conditions

such as temperature, concentration and solvent. However, an enantiomerically pure standard with known absolute configuration is required, which is not always possible. A suitable X-ray diffraction technique may be used to identify the absolute configuration of chiral molecules if good quality crystals can be made. Another way is to correlate the configuration by chemical transformation to a known compound, a process that is often not practical.

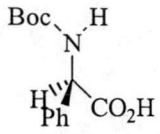
Enantiomers cannot be distinguished in an achiral medium by their NMR spectra because their resonances are chemical shift equivalent. In contrast, diastereomers may be distinguished because certain resonances are chemical shift non-equivalent. Determination of enantiomeric purity using NMR spectroscopy requires the intervention of a chiral auxiliary to convert an enantiomeric mixture into a mixture of diastereomers. Provided that the magnitude of the observed chemical shift non-equivalence is sufficient to give baseline resolution, integration of the appropriate signals gives a measure of the diastereomeric composition. This can be directly related to the enantiomeric composition of the original mixture. Three types of chiral auxiliary are widely used. Chiral derivatizing agents (CDAs) form diastereomers while chiral solvating agents (CSAs) and chiral lanthanide shift reagent (CLSRs) form diastereomeric complexes *in situ* with the substrate enantiomers.

With a suitable model, the absolute configuration of α-substituted alcohol and primary amines can be determined by the NMR technique.[41] This consists of the derivatization of the amines of unknown configuration with the *R* and *S* enantiomers of a chiral derivatizing reagent and subsequent comparison of the NMR spectra of the resulting diastereomeric compounds. The configuration of amine can be reliably established by means of a model that correlates the configuration of the amine with the sign of the differences observed in the chemical shifts ($\Delta\delta^{R,S}$) of the substituents bonded directly to the chiral center (L_1/L_2).

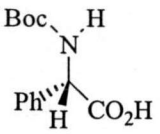
3.9.2 Boc-phenylglycine (BPG) as chiral derivatizing reagent

Boc-phenylglycine (BPG) had recently been recommended by Riguera[42] as a suitable chiral derivatizing reagent for amines for determination of absolute configuration. Its structure incorporates a phenyl ring as anisotropic group, NH-Boc acts as the polar group, which helps fixing the resulting amide in a specific and

predictable conformation, and the carboxyl provides a linkage to the amine (*via* amide bond). Furthermore, the two enantiomers (*R*)- and (*S*)-BPG, are inexpensive and commercially available in optically pure form.



(*R*)-Boc-phenylglycine
(*R*)-BPG



(*S*)-Boc-phenylglycine
(*S*)-BPG

Figure 3.3 The two enantiomers of (*R*)- and (*S*)-BPG by Riguera[42]

Riguera's[42] Molecular Mechanics calculations indicated that the *anti*-periplanar (*ap*) conformation of Boc-phenylglycineamides is more stable than the *syn*-periplanar (*sp*) conformation by 1.76 kcal/mol. The calculations also indicate that it is the most stable conformer.

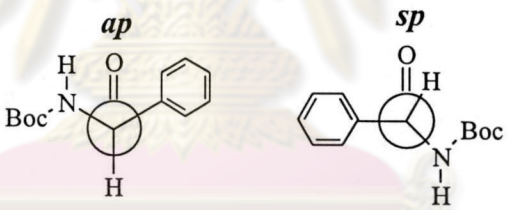


Figure 3.4 The low-energy rotamers around the C_α-CO bond in BPG amides by Riguera[42]

Moreover, Riguera[42] found that in the most preferred conformation of Boc-phenylglycine amides, the L_1 substituent in the (*R*)-BPG amides should be shielded by the anisotropic effect of the Ph ring of BPG in the *ap* conformation, while the L_2 substituent will remain unaffected (**Figure 3.5a**). In the case of the (*S*)-BPG amides, it is L_2 that is shielded in the *ap* conformer with L_1 remaining unaffected (**Figure 3.5b**). Therefore, L_1 will be more shielded in the (*R*)-BPG amide than in the (*S*)-analogue, and conversely, L_2 will be more shielded in the (*S*)-BPG amides than in the (*R*)-analogue.

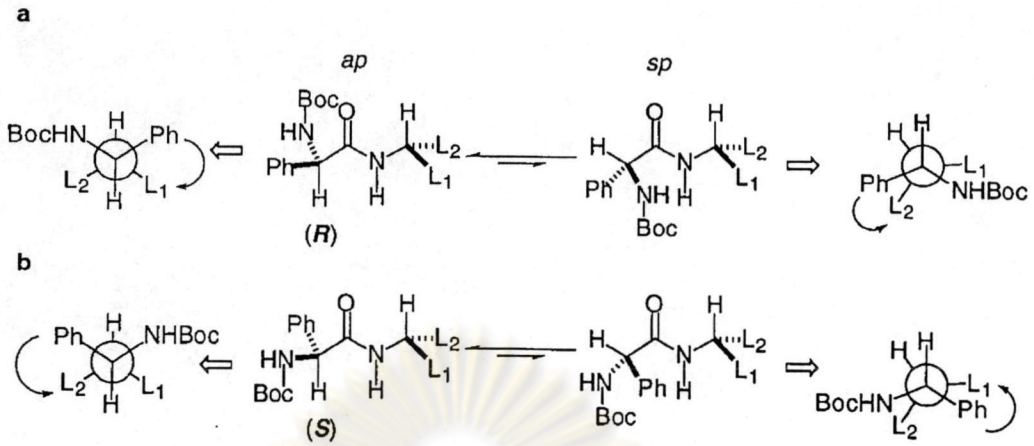
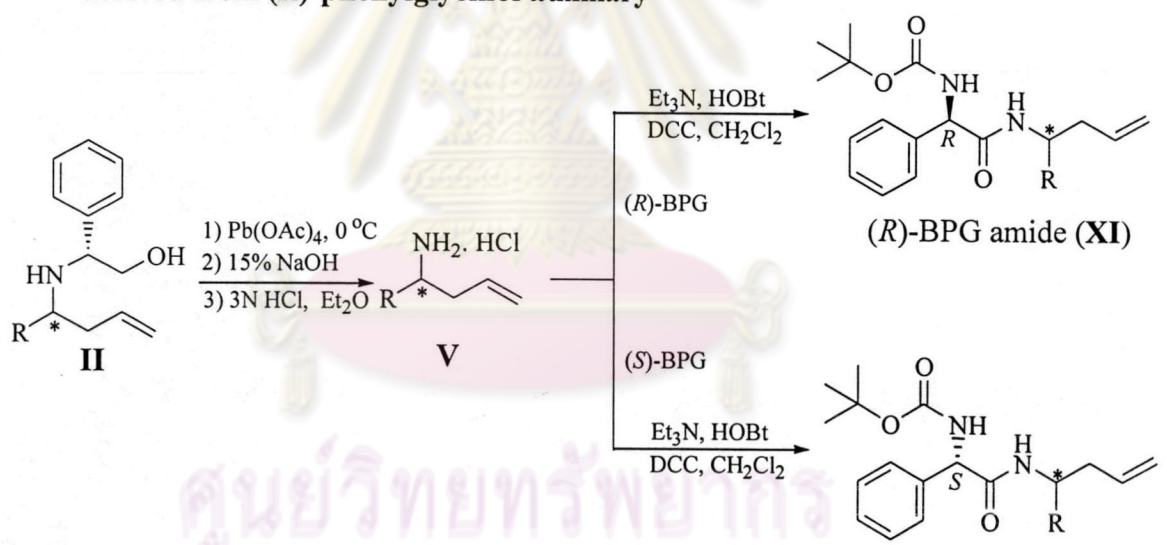


Figure 3.5 Equilibrium between the *ap* and *sp* conformers of
a) (*R*)-BPG amides
b) (*S*)-BPG amides
By Riguera[42]

3.9.3 The assignment of the absolute configuration of the homoallylic amines derived from (*R*)-phenylglycinol auxiliary



R= Ph (**V-6**, **XI-1**, **XII-1**); ^{i}Pr (**V-7**, **XI-2**, **XII-2**)

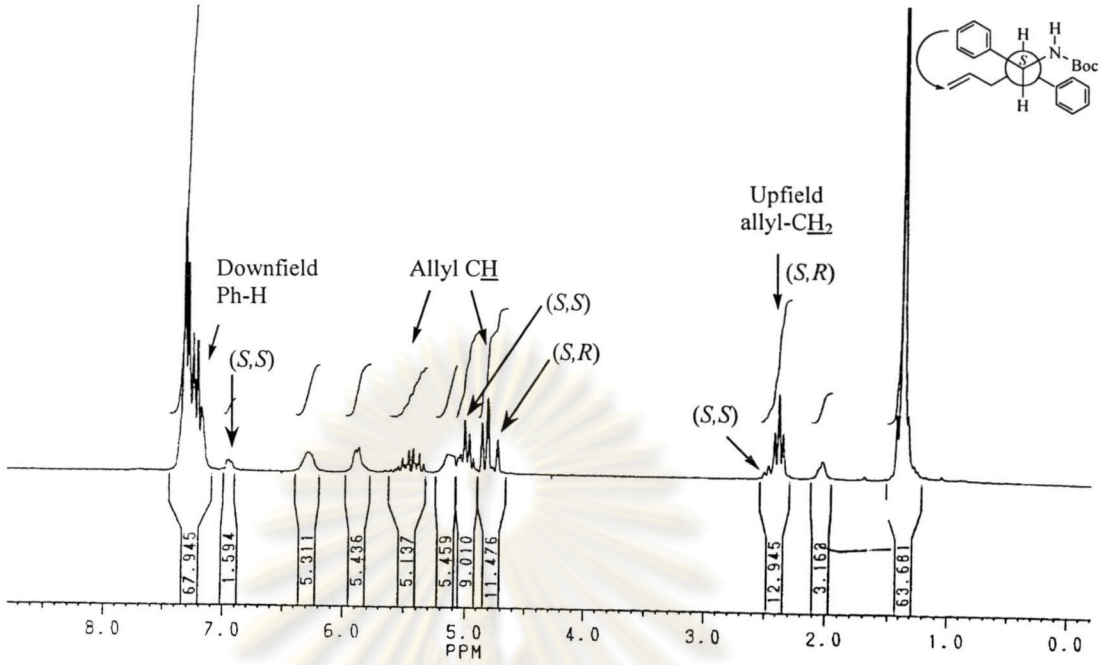
Scheme 3.24

Initially the homoallylic amine (**V-6**) was deprotected with $Pb(OAc)_4$ followed by treatment with aq HCl/Et_2O (**Section 3.8.3b**). The preparation of diastereomeric amides were prepared from the resulting amine and (*R*)- and (*S*)-BPG by treatment with DCC, HOBt and Et_3N in CH_2Cl_2. The reaction mixture was filtered to remove the dicyclohexylurea, and the amide was purified by flash chromatography on silica

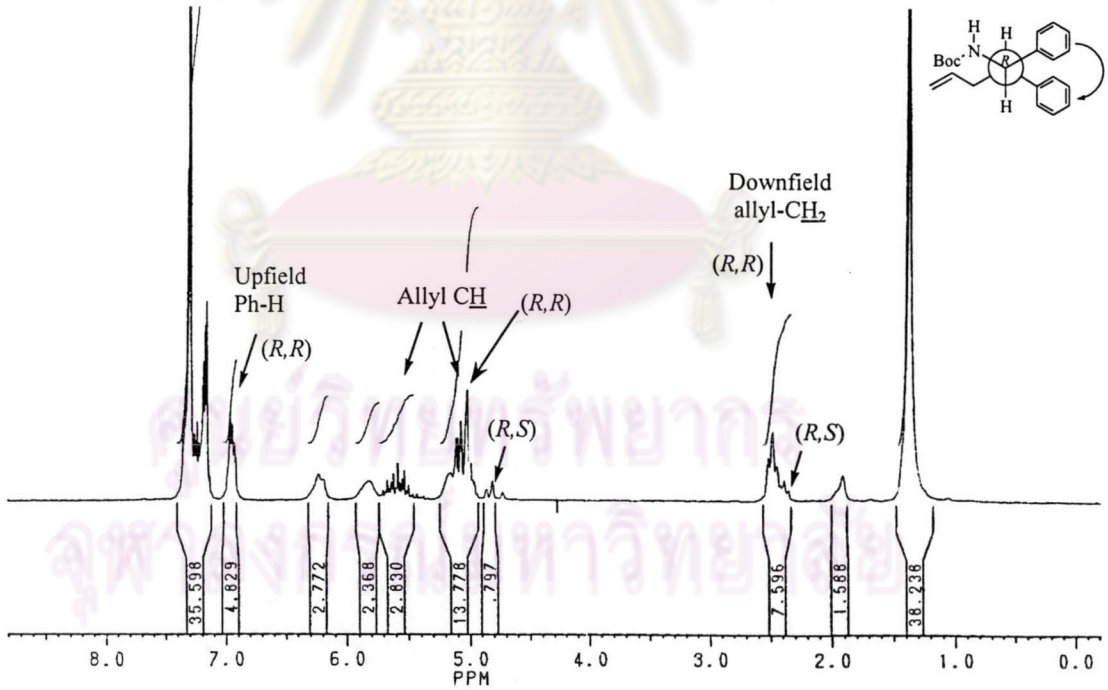
gel using hexane/ethyl acetate as eluant. The products (*R*)-BPG amide **XI-1** and (*S*)-BPG amide **XI-1** were obtained in 44 and 53 % yield respectively.

^{1}H-NMR spectrum of the amide derived from 1-phenylbut-3-enylamine (R = Ph) and (*S*)-BPG showed a marked upfield shift of the allyl group signal (**Figure 3.6a**) as compared to the corresponding (*R*)-BPG amide derivative, suggesting that the allyl group takes the L_1 position (**Figure 3.6b**). In addition, the *ortho*-protons of the phenyl group in the (*R*)-BPG amide derivative appeared at a more upfield position than the corresponding signal in the (*S*)-BPG amide derivative therefore the phenyl group should occupy the L_2 position. According to the model by Riguera[42] (**Figure 3.5**), the configuration of the homoallylic amine (R = Ph) derived from (*R*)-phenylglycinol has been assigned as "*R*". The corresponding homoallylic amine derived from (*S*)-phenylglycinol gave opposite NMR spectra upon derivatization with BPG, therefore its configuration is "*S*".

However, on careful investigation of the spectra in each case, a small amount of the compound with opposite configuration was observed (marked by (*R/S, R/S*) in the spectra) which indicated that a partial racemization took place, to the extent of 30 % in the case of R = Ph and 20 % for R = ^{i}Pr.

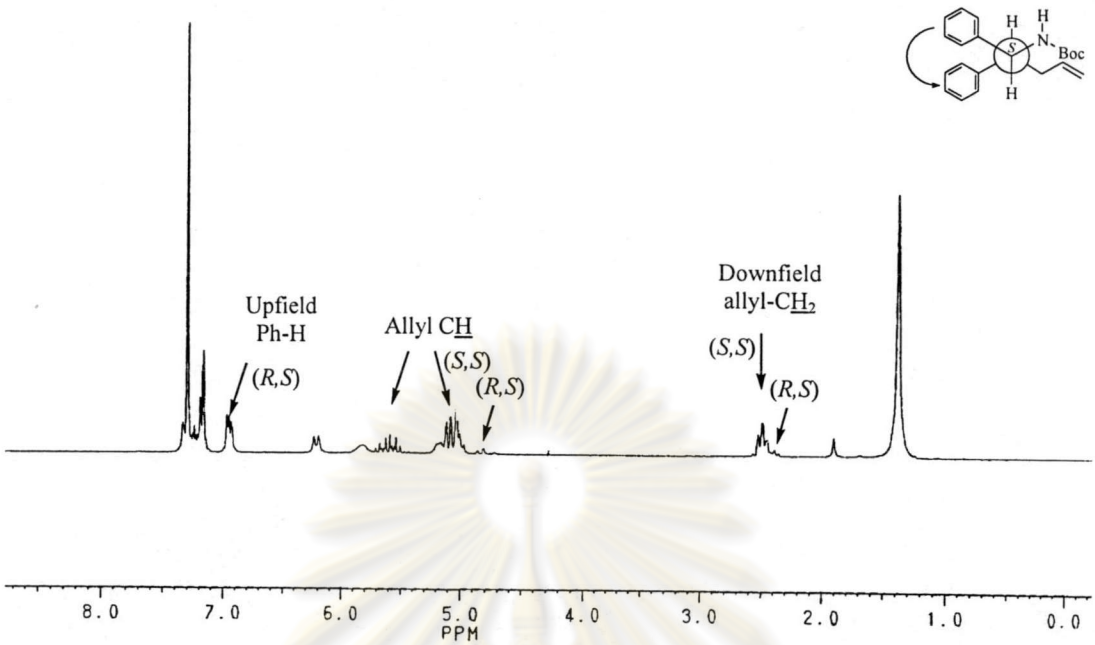


(a) ^{1}H-NMR spectrum of 1-phenylbut-3-enylamine derived from (*R*)-phenylglycinol auxiliary after derivatization with (*S*)-BPG

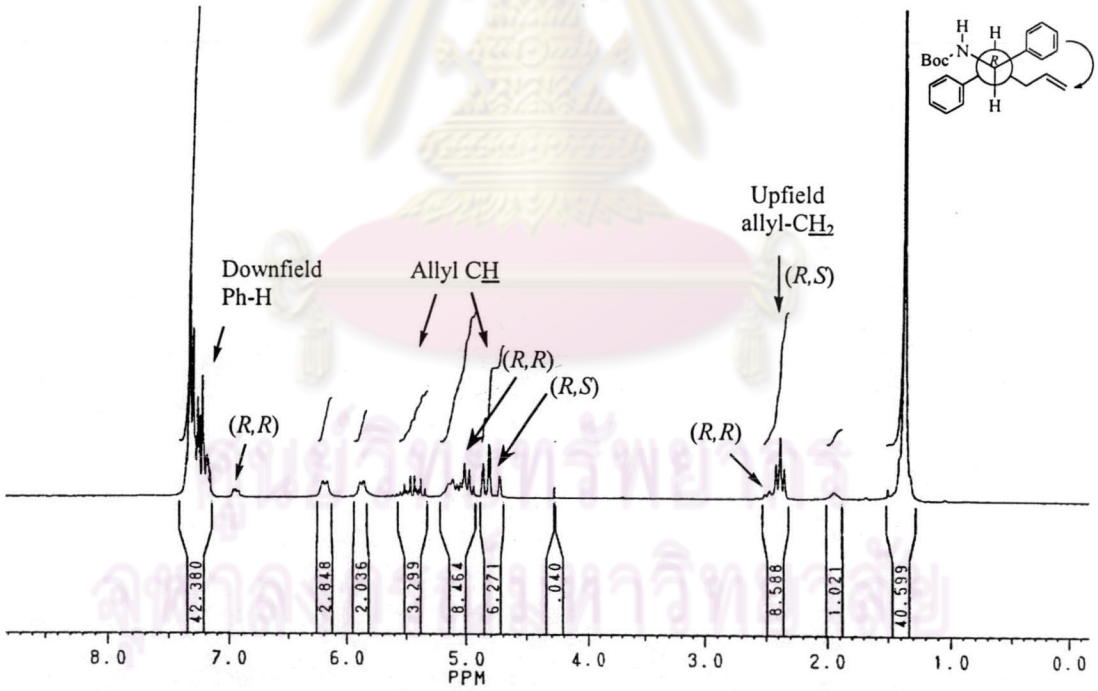


(b) ^{1}H-NMR spectrum of 1-phenylbut-3-enylamine derived from (*R*)-phenylglycinol auxiliary after derivatization with (*R*)-BPG

Figure 3.6 ^{1}H-NMR spectrum of 1-phenyl-but-3-enylamine derived from (*R*)- and (*S*)-phenylglycinol auxiliary after derivatization with (*R*)- and (*S*)-BPG from the oxidative cleavage by lead tetraacetate and 3N HCl

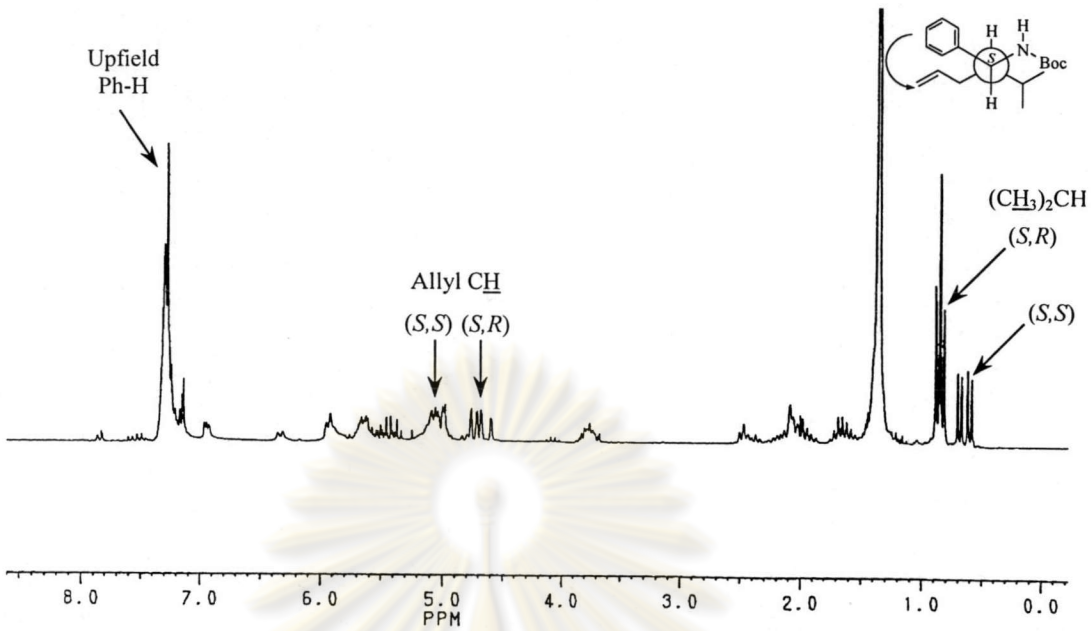


(c) ^{1}H-NMR spectrum of 1-phenylbut-3-enylamine derived from (*S*)-phenylglycinol auxiliary after derivatization with (*S*)-BPG

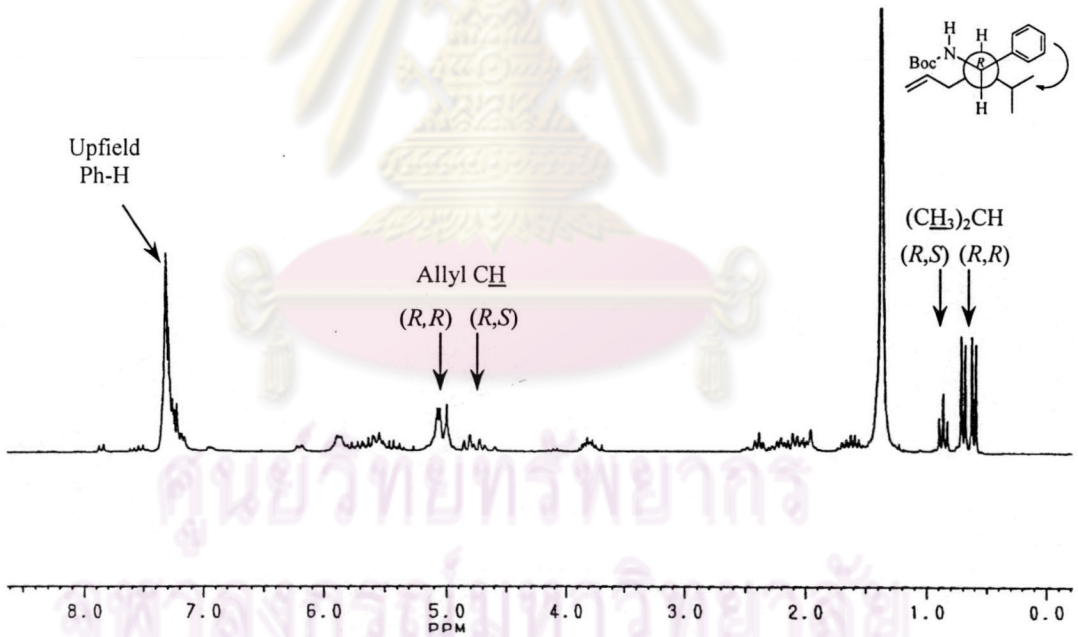


(d) ^{1}H-NMR spectrum of 1-phenylbut-3-enylamine derived from (*S*)-phenylglycinol auxiliary after derivatization with (*R*)-BPG

Figure 3.6 ^{1}H-NMR spectrum of 1-phenyl-but-3-enylamine derived from (*R*)- and (*S*)-phenylglycinol auxiliary after derivatization with (*R*)- and (*S*)-BPG from the oxidative cleavage by lead tetraacetate and 3N HCl (Continued).



(a) ^{1}H-NMR spectrum of 1-isopropylbut-3-enylamine derived from (*R*)-phenylglycinol auxiliary after derivatization with (*S*)-BPG



(b) ^{1}H-NMR spectrum of 1-isopropylbut-3-enylamine derived from (*R*)-phenylglycinol auxiliary after derivatization with (*R*)-BPG

Figure 3.7 ^{1}H-NMR spectrum of 1-isopropyl-but-3-enylamine derived from (*R*)- and (*S*)-phenylglycinol auxiliary after derivatization with (*R*)- and (*S*)-BPG from the oxidative cleavage by lead tetraacetate and 3N HCl

3.10 The assignment of the absolute configuration of the homoallylic amines derived from (*R*)-phenylglycinol auxiliary by using $Pb(OAc)_4$/ NH_2OH

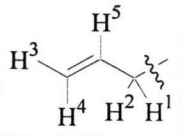
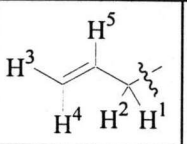
With such a high degree of racemization, it is not safe to attempt to deduce the absolute configuration. As a result, the new deprotection method using $Pb(OAc)_4$/ NH_2OH was employed (**Section 3.8.3c**). Seven homoallylic amines with different substituents **V-(6-12)**, both aliphatic and aromatic **Table 3.10**, were chosen as model compounds. These were derivatized with (*R*)- and (*S*)-BPG and absolute configuration determined as described earlier (section **3.9.3**).

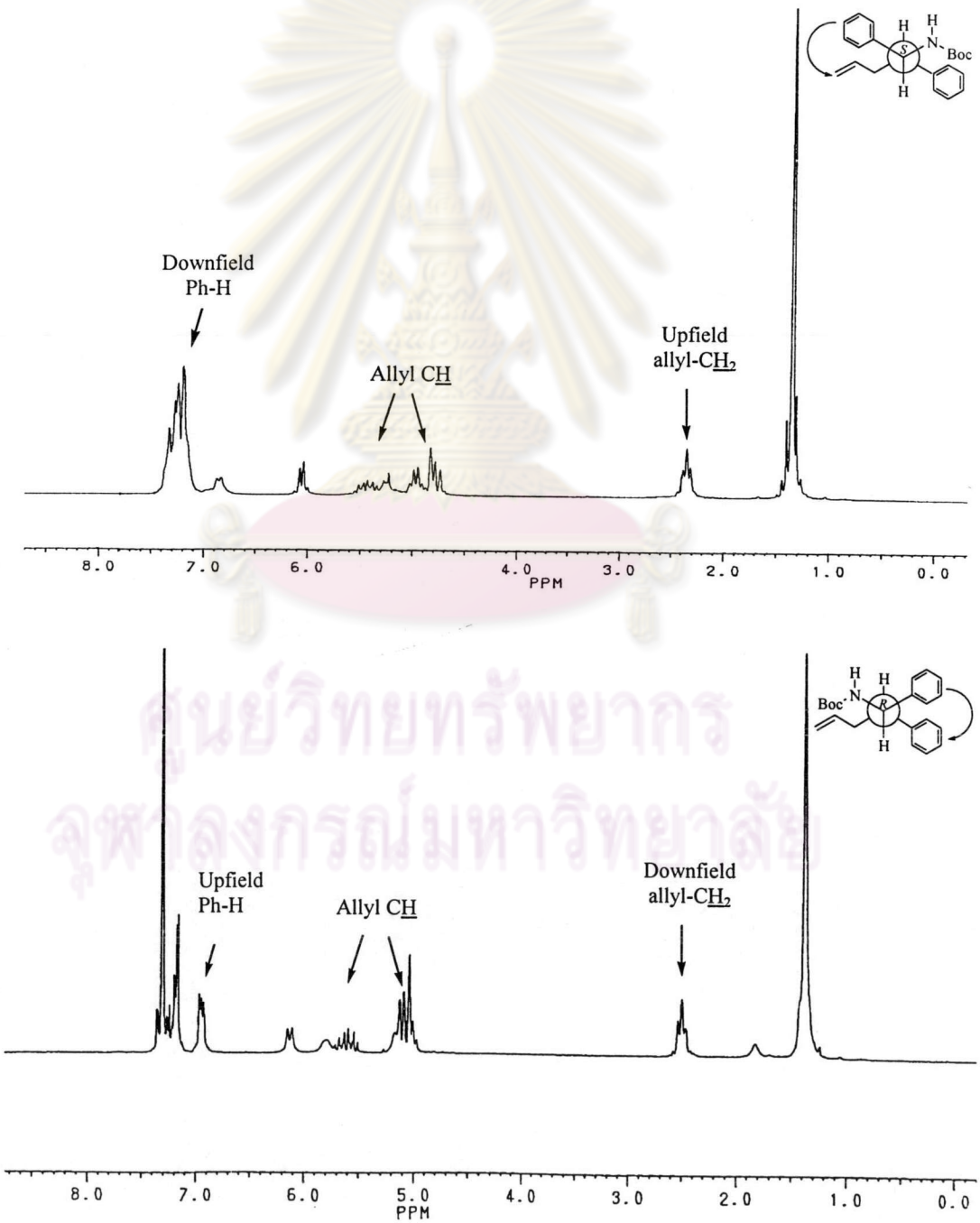
Table 3.11 The absolute configuration of the homoallylic amines

Entry	R	*R*-BPG amide		*S*-BPG amide		Config.	*ds* (*R* : *S*)[a]
		Product	Yield (%)	Product	Yield (%)		
1	Ph	**XI-1**	52	**XI-1**	61	***R***	> 99 : 1
2	2-Pyridyl	**XI-4**	56	**XI-4**	50	***R***	> 99 : 1
3	2-$OMeC_6H_4$	**XI-3**	51	**XI-3**	40	***R***	80 : 20[b]
4	^{i}Pr	**XI-2**	50	**XI-2**	68	***R***	> 99 : 1
5	^{n}Pr	**XI-6**	61	**XI-6**	63	***S***	> 99 : 1[c]
6	^{c}Hex	**XI-5**	59	**XI-5**	62	***R***	> 99 : 1
7	Cinnamyl	**XI-7**	87	**XI-7**	55	***R***	> 99 : 1

[a] Determined from 200 MHz ^{1}H-NMR spectra of the product after derivatization with (*R*)- and (*S*)-Boc-phenylglycine; [b] The starting material was a 80:20 mixture of *RR*:*RS* diastereomers; [c] The absolute configuration must be assigned as *S*. In fact the spatial arrangement of all substituents are the same as other compounds, but the lower priority of the ^{n}Pr group as compared to allyl group according to the CIP sequence rule makes the stereochemical designation *S* rather than *R*.

Table 3.12 The absolute configuration of the homoallylic amines R=Phenyl

R	H	δ-(*S*)-BPG		δ-(*R*)-BPG		Config.
						
Ph From (*R*)- phenylglycinol	1, 2 3, 4 5	2.37 4.73 5.43	7.16	2.45 5.10 5.58	6.92	***R***



The configurations of other homoallylic amines were determined similarly. In all cases, the (*R*)-phenylglycinol auxiliary gave the homoallylic amines with (*R*)-configuration regardless of the nature of substituent. Thus it is quite safe to assume that the remaining compounds have the same with (*R*)-configuration except **V-11** (R = ^{n}Pr) and all other compounds bearing primary alkyl substituent because of the lower priority of R group as compared to allyl group according to the CIP sequence rule makes the stereochemical designation *S* rather than *R*.

3.11 The transition state model to explain the selectivity

The observed stereoselectivity of the allyladdition to imine, benzaldehyde and (*R*)-phenylglycinol as a chiral auxiliary, appeared to follow the chelation model. There are four possible transition states leading to two diastereomeric products.

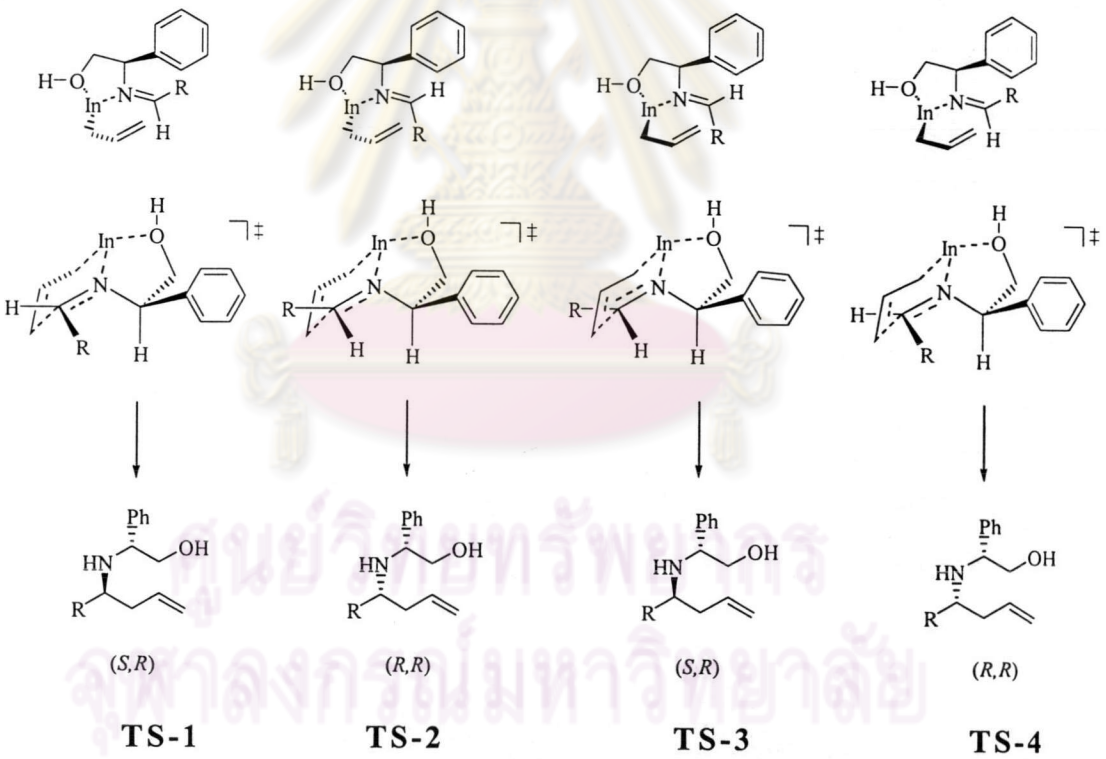


Figure 3.8 The transition state model of the allyl addition to imine
TS-1 The (*Z*)-imine allyl addition on the opposite face to the Ph group.
TS-2 The (*E*)-imine allyl addition on the opposite face to the Ph group.
TS-3 The (*E*)-imine allyl addition on the same face to the Ph group.
TS-4 The (*Z*)-imine allyl addition on the same face to the Ph group.

The priority of the functional groups was determined to be: NH=1, R=2 and allyl=3 respectively. The configuration of the **TS-2** and **TS-3** has the C=N of the imine in *E*-form so they should be more stable than **TS-1** and **TS-4**

In **TS-2** the allyl group adds on the opposite face (*re*-face for CIP rank NH = 1, R = 2 and allyl = 3) relative to the phenyl group on the auxiliary thus it should be lower in energy based on steric ground compared to **TS-3**. **TS-2** would lead to (*R*)-configuration which is in accordance with the experimental results.