CHAPTER I

INTRODUCTION

1.1 Introduction

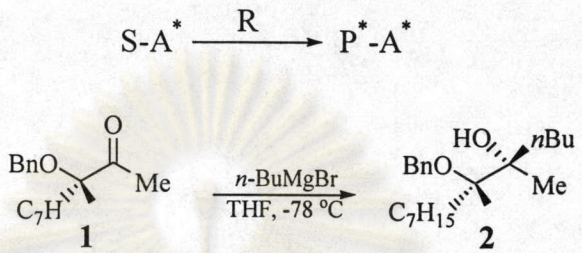
The amine group is one of the fundamental structures in organic chemistry. In particular enantiomerically pure amines bearing a stereogenic center at the α-position play a crucial role as characteristic structural features in bioactive natural products and pharmaceutically important compounds.[1] Carbon-carbon bond formation by nucleophilic addition of carbon nucleophiles to imines is an important tool for synthesizing more complex biologically active nitrogen containing compounds.[2,3] While additions of carbon nucleophiles to carbonyl compounds have been extensively investigated and well established, considerably less successful results were obtained in the analogous reactions with imines. The development of these additions has been severely limited both by the poor electrophilicity of imine toward nucleophilic addition and the facile abstraction of acidic α-protons resulting in imine-enamine tautomerization.

To circumvent these two problems, a variety of methods have been developed in recent years. This has greatly improved the scope of organometallic additions to imines or imine derivatives. The electrophilicity of the carbon atom of the C=N bond can be increased by *N*-alkylation, *N*-oxidation, *N*-acylation or *N*-sulfonation to give more reactive iminium salts, reactive nitrones, acylimines and sulfonimines respectively. However, these methods require the introduction and removal of the activating groups to generate free amines, which are not always easy. For this reason, another strategy has involved activation of the C=N bond of imines or imine derivatives by coordination of a Lewis acid with the nitrogen lone pair. The use of the more reactive, resonance-stabilized allyl organometallics reagents in imines addition reactions has also supplied a partial solution to these problems. Incidentally, the resulting homoallylic amines are useful intermediates for the synthesis of several important classes of biologically active compounds such as β-amino acids, pyrrolidines, etc.

1.2 Strategies for asymmetric synthesis[4]

There are a number of strategies that can be utilized to generate new asymmetric centers in molecules thus can be divided into four main types:

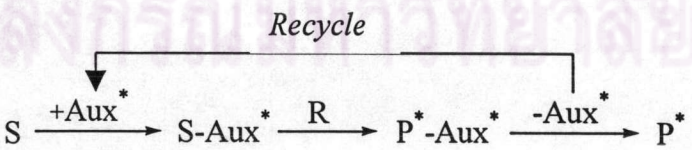
1.2.1 Substrate control

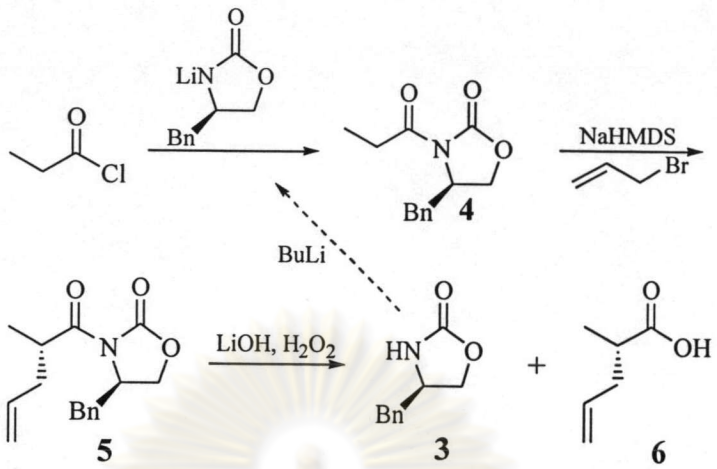


Scheme 1.1

Also known as a 'first generation method', this approach involves the use of an achiral substrate or portion of a molecule (S) with a chiral group or asymmetric center (A^*) covalently attached nearby. The chiral influence is close enough so that the subsequent reaction with an achiral reagent (R) is effectively controlled by A^*, which induces asymmetry in the substrate portion (S) of the molecule to provide the product (P^*) with the new stereogenic center(s). The chiral group A^* is retained in this process and, in most cases, throughout the synthesis. In **Scheme 1.1**, the chiral ketone **1** is converted into the alcohol **2** by a simple nucleophilic addition to a carbonyl group. In this reaction, the stereogenic center marked is introduced with good selectivity.

1.2.2 Auxiliary control

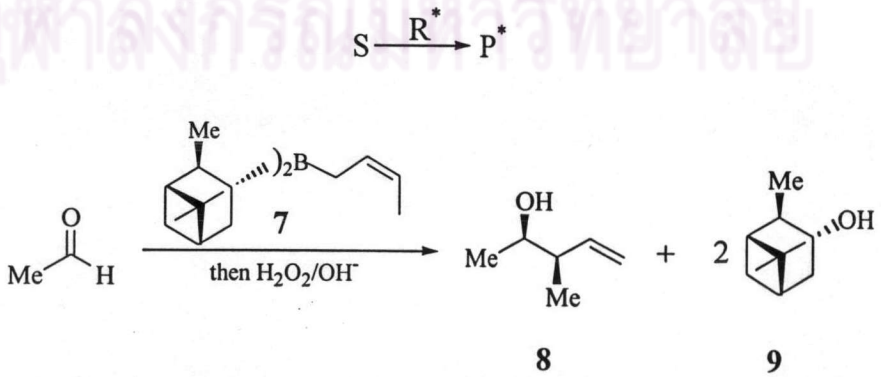




Scheme 1.2

In this case a temporary chiral influence of 'chiral auxiliary' (Aux^*) is covalently bound to the substrate (S), normally by a weaker C-O or C-N bond which can be cleaved in a later step. The substrate-auxiliary ($S\text{-}Aux^*$) molecule is then treated with an achiral reagent, and an asymmetric reaction, controlled by the auxiliary occurs and give the product (P^*) which now contains asymmetry. The chiral auxiliary (Aux^*) is then removed in a subsequent step to give the desired product and the auxiliary, which in some cases can be recycled by attachment to more of the substrate. In **Scheme 1.2**, the chiral auxiliary is the oxazolidine **3** derived from an amino acid. The achiral substrate is attached to give the substrate-auxiliary intermediate **4** which undergoes an asymmetric alkylation to provide product **5**. The auxiliary is then removed by hydrolysis to give the acid product **6** and the neutral auxiliary, ready to be recycled.

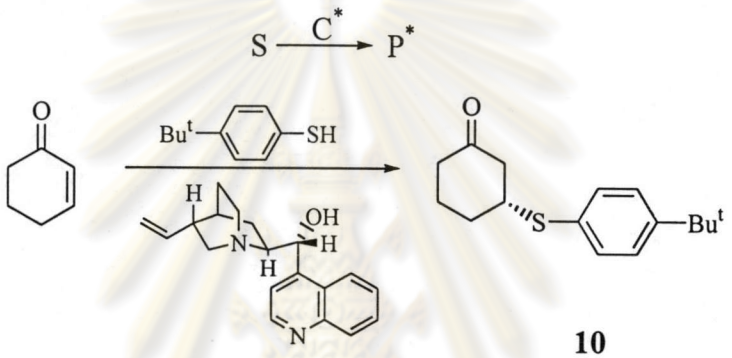
1.2.3 Reagent control



Scheme 1.3

In this method, a chiral reagent (R^*) is allowed to react with an achiral substrate (S) to produce a chiral product (P*). The chirality of the reagent is transferred to the substrate. As shown in **Scheme 1.3** the chiral crotyl boron reagent **7** attacks acetaldehyde exclusively from the *Si* face where the double bond geometry dictates the relative stereochemical outcome. This results in the production of the *syn*-propionate product **8** as well as two molar equivalents of alcohol **9** derived from the chiral auxiliary part of the reagent.

1.2.4 Catalyst control[5]



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Scheme 1.4

The final method is catalyst control where a chiral catalyst (C^*) is allowed to react with an achiral substrate (S) to produce a chiral product (P^*). The advantages over first- and second-generation methods are two-fold: the range of starting materials is far wider, since it needs no longer to come from the chiral pool, and there is no two dedicated steps to the installation and removal of a chiral auxiliary. **Scheme 1.4** shows the asymmetric conjugate addition of a thiophenol to cyclohexenone to give **10** catalysed by the alkaloid cinchonidine. In particular, catalytic asymmetric oxidation and hydrogenation are very well established and have been widely used from research laboratory to industrial synthesis of chiral compounds. The importance of this type of asymmetric synthesis is emphasized by the awarding of the 2001 Nobel prizes to Sharpless, Noyori and Knowles, the pioneers of this field.

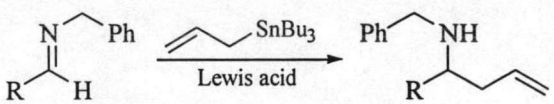
1.3 Literature review of the allylation of imines

1.3.1 Use of allylic organometallic reagents

Reaction of allylic organometallic compounds with imines provides a potentially valuable route to homoallylic amines, which are of particular interest owing to the various possible transformations of the C=C double bond of the allyl moiety. Allylic organometallic reagents are in general more reactive than nonstabilized organometallic compounds for imine addition reactions. A greater ionization of the carbon-metal bond, due to the resonance stabilization of the allyl anion, has been suggested to explain this increase in reactivity.[2] However, owing to α-deprotonation, reactions involving basic lithium, magnesium, and zinc allylic reagents are limited to imines derived from nonenolizable or α-alkyl-substituted aliphatic aldehydes. Milder allylating species such as allyl boranes, allylsilanes, allyl stannanes and allyl metals derived from less familiar metals such as Nb, Ti and In. have been investigated in recent years and were found to be superior to allyl Grignard or lithium in many cases. Furthermore, Barbier-type allylation of imine, involving the formation of the allylmetal reagent *in situ*, has been the subject of significant advances in recent years.[46]

In this section, some selected allylation reactions employing various organometallic reagents (except indium) will be discussed. For the well established use of allyl Grignard, allyl boranes and allyl silanes, the readers should consult a review by Yamamoto.[6]

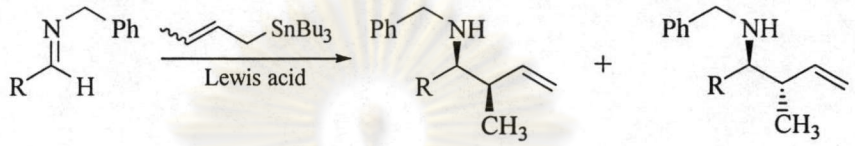
In 1985, Keck and Enholm[7] presented the Lewis acid-mediated addition of allyltri-*n*-butylstannane to simple achiral aldimines (**Scheme 1.5**). The addition of allyltri-*n*-butylstannane and Lewis acid such as $BF_3{\cdot}Et_2O$ or $TiCl_4$ to aldimine, afforded the desired products in reasonable to good yields.



R = ^{c}Hex, $BF_3{\cdot}Et_2O$, 48 %; $TiCl_4$, 81 %
R = Ph, $BF_3{\cdot}Et_2O$, 73 %; $TiCl_4$, 53 %
R = 2-furyl, $BF_3{\cdot}Et_2O$, 61 %; $TiCl_4$, 88 %

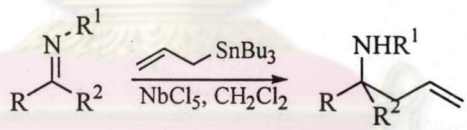
Scheme 1.5

Keck[7] has studied the additions of crotyltri-*n*-butylstannane to aldimines using various Lewis acids (**Scheme 1.6**). All Lewis acids that successfully promoted reaction gave *ca.* 4:1 mixtures of diastereomeric products in which the *syn*-product predominated. For the case of R = ^{c}Hex, *syn*:*anti* ratios were 77:23 and 79:21 for all of the following Lewis acids: $BF_3{\cdot}Et_2O$ (82 %), $TiCl_4$ (83 %), $MgBr_2$ (71 %), Et_2AlCl (79 %) and $ZrCl_4$ (84 %).



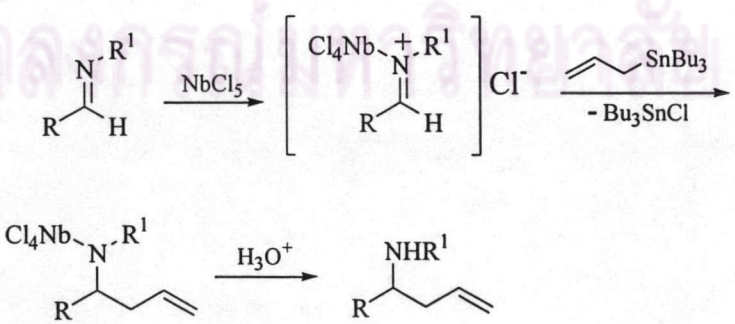
Scheme 1.6

In 2002, Andrade and co-workers[8] presented the use of $NbCl_5$ as a Lewis acid in the allylation reaction of various imines with allyltributylstannane (**Scheme 1.7**). The conditions for the $NbCl_5$-mediated allylation of imines are CH_2Cl_2 as the solvent, at –15 °C and excess of the allylstannane. Under these conditions a variety of aromatic aldimines were allylated in reasonable to good yields (59-85 %).



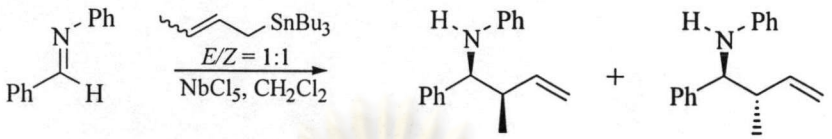
Scheme 1.7

The activation of the imines probably occurs *via* the formation of an iminium salt with $NbCl_5$.[8] (**Scheme 1.8**)



Scheme 1.8

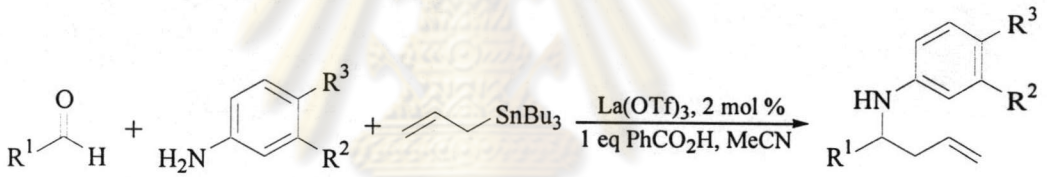
The stereo- and regioselectivity of these $NbCl_5$-promoted allylation reactions were assessed in the reaction between 2 equiv. of crotylstannane (3-methylallylstannane, 1:1 mixture of isomers) and *N*-benzylideneaniline in CH_2Cl_2 (**Scheme 1.9**).



Scheme 1.9

The allylated products were obtained in 60-62 % yields and excellent diastereoselectivities (*syn: anti* = 90-98 %). At –78 °C, the *syn* isomer was obtained almost exclusively, regardless of the stereochemistry of the stannane double bond.

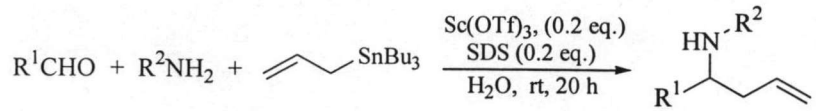
Furthermore, Greeves and co-worker[9] reported three-component synthesis of homoallylic amines by using lanthanum triflate-benzoic acid catalysts.



R^1 = Ph, R^2 = Me, R^3 = H; 67 % yield
R^1 = 4-MeSC$_6$H$_4$, R^2 = Me, R^3 = H; 89 % yield
R^1 = Ph, R^2 = H, R^3 = Me; 87 % yield
R^1 = 4-MeSC$_6$H$_4$, R^2 = H, R^3 = Me; 76 % yield

Scheme 1.10

In 1998, Kobayashi[10] reported that the three-component reactions of aldehydes, amines and allyltributylstannane (**Scheme 1.11**). The reaction proceeded smoothly in water without using any organic solvents, in the presence of a small amount of scandium triflate [$Sc(OTf)_3$] and sodium dodecylsulfate (SDS), to afford the corresponding homoallylic amines in high yields (66-90 %).

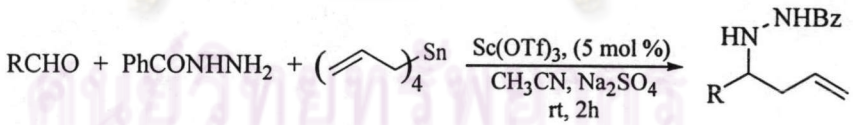


R^1 = Ph, R^2 = Ph; 83 %
R^1 = 2-Furyl, R^2 = 4-ClC_6H_4; 90 %
R^1 = $Me(CH_2)_7$, R^2 = 4-ClC_6H_4; 66 %

Scheme 1.11

Kobayashi had proposed that the imine formation from aldehydes and amines was very fast in the presence of both $Sc(OTf)_3$ and SDS, and that the selective activation of imines rather than aldehydes was achieved using $Sc(OTf)_3$ as a catalyst. It is also noteworthy that using a small amount of a surfactant created sufficient hydrophobic reaction environment to achieve the dehydration and addition reactions in water.

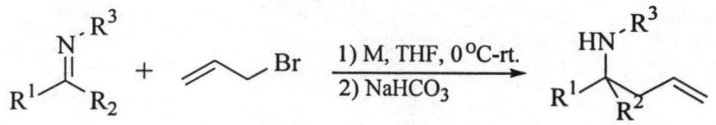
Later, in 1999, Kobayashi[11] reported that in the presence of a catalytic amount of scandium triflate (1-5 mol %), benzoylhydrazones reacted with tetraallylstannane to afford the corresponding homoallylic hydrazines (**Scheme 1.12**). Three-component reactions of aldehydes, benzoylhydrazine, and tetraallylstannane also proceeded smoothly in the presence of a catalytic amount of scandium triflate. Hydrazones are less electrophilic than imines, but they are also much more stable towards hydrolysis.



R = C_6H_{13}, $(CH_3)_2CHCH_2$, ^{c}Hex, Ph, PhCH=CH (84-99 %)

Scheme 1.12

In 1996, Hou and co-workers[12] reported the allylation of both aldimines and ketimines under simple 'Barbier-type' conditions whereby the allylation species were generated *in situ* from allyl bromide and commercial magnesium foil or commercial zinc powder in THF at room temperature in very high yield (**Scheme 1.13**).

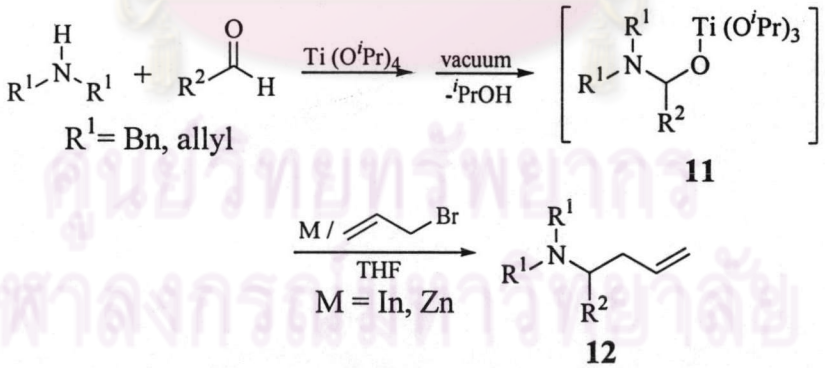


R^1=Ph, R^2= H, R^3=Bn; M=Mg, 92 %yield; M=Zn, 95 %yield

Scheme 1.13

However, when chiral imines derived from (*S*)- or (*R*)-1-phenylethylamine were used, the diastereoselectivity was poor (1:1 to 2.5:1). The diastereomeric ratios obtained by 300 MHz ^{1}H NMR spectra and the configuration was not determined.

In 2002, Mosset and co-workers[13] have found that the homoallylamines can be obtained in a one-pot synthesis directly from an aldehyde and a secondary amine (**Scheme 1.14**). They devised a two-step, one-pot procedure. In the first step, various aldehydes were condensed with a secondary amine such as dibenzylamine or diallylamine in the presence of titanium (IV) isopropoxide (2-3 h at 40 °C) to afford an aminoalkoxy titanium complex **11**. The liberated 2-propanol was removed by application of vacuum. In the second step, a solvent (anhydrous THF) was added followed by a metal (indium or zinc powder), and allyl bromide. After reaction (4 h at 30 °C) and work-up, homoallylamines **12** were isolated generally in good yields (58-83 %). Indium and zinc were proved to be equally effective.



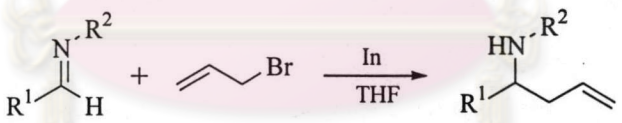
Scheme 1.14

1.3.2 Literature review of indium-mediated allylation of imines

After the success of Grignard reactions for carbon-carbon bond formation, the utilization of other metals of the Periodic system for organic synthesis has received widespread interest with indium as one of the latest additions. During the last decade, indium has emerged as a metal of high potential in organic synthesis because of its

certain unique properties. Indium metal is unaffected by air or oxygen at ambient temperatures and can be handled safely without any apparent toxicity. Indium exhibits a low heterophilicity in organic reactions and thus oxygen- and nitrogen-containing functional groups usually tolerate organoindium reagents. Moreover, indium-assisted reactions display a low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity. Because indium closely resembles magnesium, zinc and tin in several aspects, including its first ionization potential of indium metal, (5.8 eV) it could represent a suitable reagent for SET (single electron transfer) processes.[14] Indium is very soft, plastic-like and can easily be bent. The metal (m.p. 157 °C) belongs to the series of low melting solid elements such as gallium, cadmium, tin, bismuth and alkali metals. In addition, organoindium reagents possess an interesting feature such that they are relatively stable in the presence of water and air, allowing their reactions to be performed without requiring strictly anhydrous conditions nor inert atmosphere.

In 1992, Mosset and co-workers[15] reported the Barbier-type allylation of imines, involving the formation of the allylmetal reagent *in situ* (**Scheme 1.15**). The aldimines are efficiently allylated by using a mixture of allylbromide and indium powder in anhydrous tetrahydrofuran (THF) under inert atmosphere.

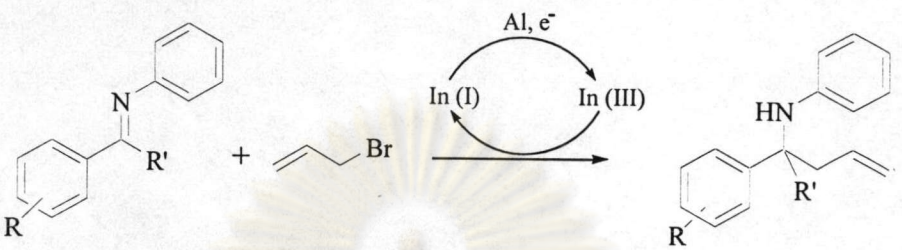


Scheme 1.15

Aldimines prepared from an aromatic amine reacted in fair to good yields (42-91 %) with short reaction time. On the other hand, when R^2 has an sp^3 carbon linked to nitrogen, yields were substantially lower (32-49 %) and longer reaction time was required. The γ-substituted allyl halides afforded the branched homoallylic amines regioselectively. Furthermore, some diastereocontrol (*ca.* 4:1) was observed when a chiral imine derived from (*S*)-1-phenylethylamine was used as substrate, but the selectivity decreased (2:1) when the phenyl group was replaced by the 1-naphthyl group.

In 2002, Hilt and co-workers[16] presented a chemo-electrochemical regeneration of low valent indium (I) reagents for a Barbier-type carbon-carbon bond

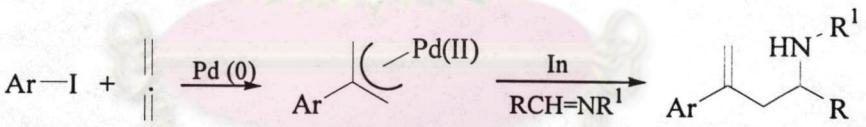
formation process for several C=N systems (**Scheme 1.16**). The homoallylic amines are obtained in good yields from aniline-derived aldimines. However, with ketimines and electron-poor aldimines, direct eletrochemical or chemical reduction becomes a competing side reaction.



R = 4-Cl, R′ = H; 95 % yield
R = 4-OMe, R′ = H; 76 % yield
R = 4-OMe, R′ = CH_3 ; 25 % yield

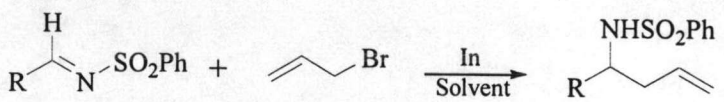
Scheme 1.16

In 2002, Grigg and co-workers[17] presented a new palladium-indium diastereoselective cascade allylation of imines using allenes and aryl iodides (**Scheme 1.17**). The allyl indium species, generated by transmetallation with π-allyl palladium (II) complexes arised from aryl iodides and allenes, reacted with imines to afford homoallylic amines.



Scheme 1.17

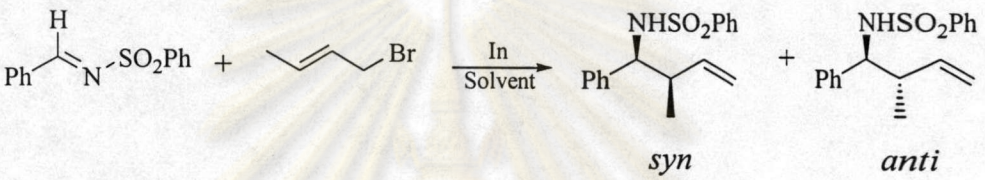
Furthermore, in 2002, Chan and co-workers[18] reported that Barbier-type allylation of sulfonimines with indium and allyl bromide can be performed smoothly in water, THF or aqueous THF (**Scheme 1.18**).



R = Ph, *p*-ClPh, *p*-MeOPh, Furyl

Scheme 1.18

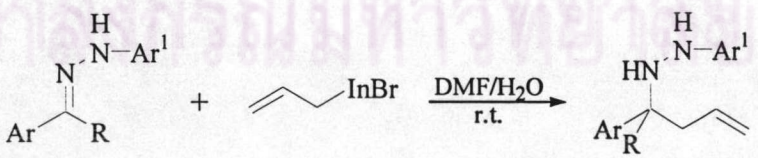
The above-mentioned Barbier-type allylation reaction of sulfonimines mediated by indium resulted in homoallylic sulfonamides in high yield (50-99 % yield in H_2O, 82-99 % yield in H_2O: THF = 1:1). In the cases where the solid sulfonimines had low solubility in water, adding some THF to the aqueous media was helpful in increasing the yields. The optimal medium for this allylation reaction seemed to be a 1:1 mixture of THF and water. Aliphatic sulfonimines were found to be generally less reactive than the aromatic sulfonimines, and the reaction needed longer reaction time with relatively lower yields obtained. The γ-allylation products were obtained exclusively from the allylation and no α-product was observed (**Scheme 1.19**).



Scheme 1.19

In the allylation of benzenesulfonimine with crotyl bromide and indium at various ratios of H_2O and THF, the stereoselectivity appeared to be quite solvent sensitive. In pure water, the product was a mixture of *anti*- and *syn*-isomers (*anti:syn* = 61:39). However, when the reaction was performed in THF or a mixture of THF and water, the reversed diastereoselectivity to moderate *syn*- selectivity was obtained.

Moreover, in 2000, Kumar and co-workers[19] showed that allylindium added to a variety of tosyl and aryl hydrazones derived from aromatic aldehydes and ketones at ambient temperature in a DMF-H_2O solvent system to afford homoallylic tosyl hydrazides and homoallylic hydrazines, respectively. Homoallylic hydroxylamines were similary prepared *via* additions of allylindium to aldonitrones.

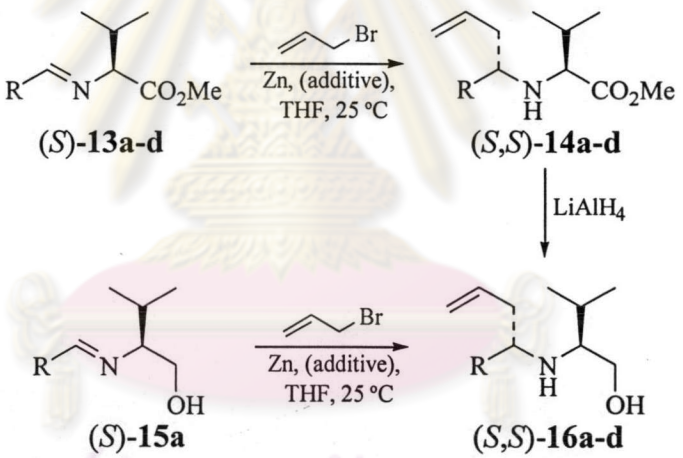


$Ar^1 = SO_2C_6H_4CH_3$, R = H
Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4 (75-89 % yield)

Scheme 1.20

1.3.3 Asymmetric allylation of imines

The addition of organometallic reagents to aldimines derived from chiral amines provides another unique option for controlling diastereoselectivity of the reaction. The heteroatom could coordinate to metal, into chiral group bound to the imine nitrogen, which might give rise, depending on the kind of metal, to different transition states and stereoselectivities. In 1993, Umani-Ronchi and co-workers[20] reported the reaction of aromatic and aliphatic imines derived from (*S*)-valine methyl ester and (*S*)-valinol with allylbromide and zinc in anhydrous THF at room temperature under argon atmosphere. A clean reaction took place with the imine (*S*)-**13a**, affording essentially (*S,S*)-**14a** with almost complete diastereoselectivity (> 99 % *de*) and with no contamination of products arising from the addition to the ester group (**Scheme 1.21**).

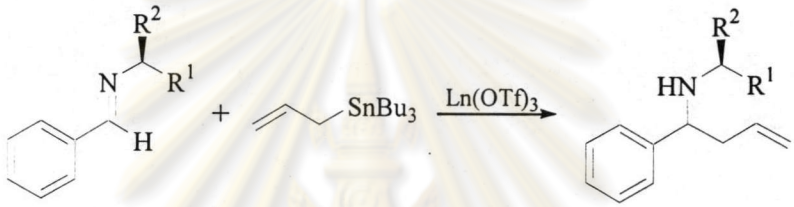


a: R = Ph; **b**: R = 4-MeO-Ph; **c**: R = 3-pyridyl; **d**: R = ^{i}Pr

Scheme 1.21

The addition of allylzinc bromide to aromatic imines was shown to be reversible, which caused the lowering of the diastereoisomeric ratio with increasing the reaction time (reaction time 0.5-32 h, *d.r.*= >99:1 to 52:48). The *retro*-allylation reaction could be avoided by performing the reaction in the presence of trace amounts of water, or by using cerium trichloride heptahydrate ($CeCl_3 \cdot 7H_2O$) as a catalyst, although at the expense of the reaction rate. Later, in 1994, Umani-Ronchi and co-workers[21] reported the addition of allylmetal, Zn, Cu, Pb, Bi, Al and In. The bimetal

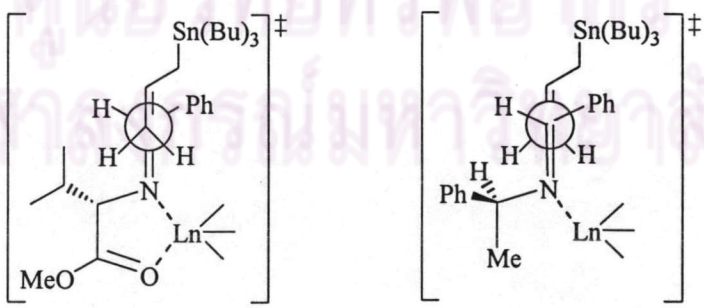
redox systems between Al and $PbBr_2$, -$SnCl_2$, –$TiCl_4$ and –$BiCl_3$ were applied to the allylation of the imines derived from methyl valinate, but satisfactory results were achieved only with Al-$BiCl_3$ and –$TiCl_4$ systems. However, the use of the Al(Hg) and Al-$PbBr_2$ systems also afforded chemo- and diastereoselectivity on the benzaldehyde imine derived from *tert*-butyl (*S*)-valinate (79 % *de*). In 1995, the same group also reported the catalytic allylation of imines promoted by lanthanide triflates with allyltributylstannane (**Scheme 1.21**).[22] It is interesting to note that the valine methyl ester auxiliary affords the prevalent formation of the (*S,S*) diastereoisomer, while the (*S*)-1-phenylethylamine gives a slight prevalent formation of the (*R,S*)-diastereoisomer.



R^1 = Ph, R^2 = Me, Ln = Yb (40 %, (*R,S* : *S,S* = 65:35)
R^1 = COOMe, R^2 = ^{i}Pr, Ln = Yb (41 %, (*R,S* : *S,S* = 18:82)
R^1 = COOMe, R^2 = ^{i}Pr, Ln = La (40 %, (*R,S* : *S,S* = 13:87)
R^1 = COOMe, R^2 = ^{i}Pr, Ln = Sc (36 %, (*R,S* : *S,S* = 9:91)

Scheme 1.22

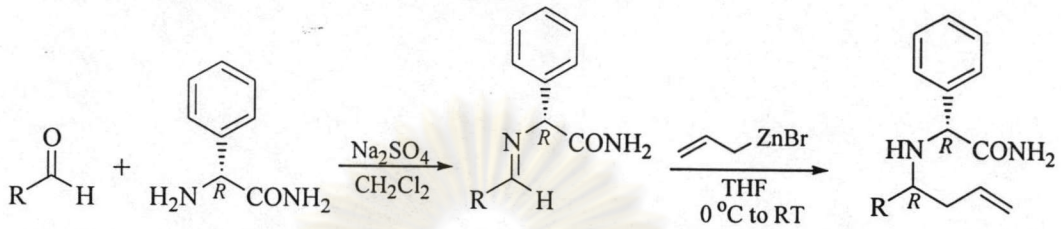
Umani-Ronchi[22] proposed the two different possible transition states shown in **Figure 1.1**. In the case of the valine methyl ester the high diastereoselection can be derived from a chelate transition state **17**.



17 **18**

Figure 1.1 The transition states of imines promoted by lanthanide triflates

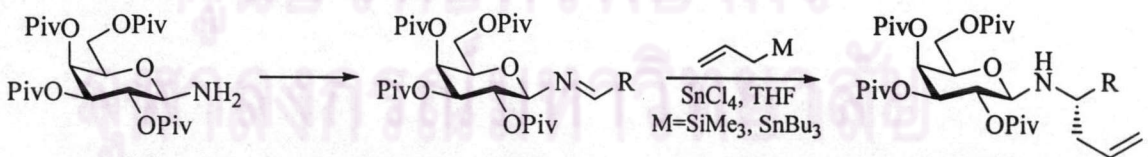
In 2001, Broxterman and co-workers[23] reported an addition of allylzinc bromide to imines derived from (*R*)-phenylglycine amide in 43-94 % yield with diastereomeric ratios > 99:1 (**Scheme 1.23**). The auxiliary can be removed by dehydration followed by a retro-Strecker and hydrolysis sequence.



R=Ph, 3-HOC_6H_4, 3-Pyridyl, ^{i}Pr, ^{n}Bu

Scheme 1.23

Kunz and co-workers[24] have utilized the complexing properties and chirality of carbohydrates in diastereoselective reactions of *O*-pivaloylated-*N*-galactosylimines with allylsilanes and allylstannanes. With allyltrimethylsilane in the presence of $SnCl_4$, imines **19** derived from aromatic and heteroaromatic aldehydes were converted to homoallylamines **20**, giving ratios of diastereomers higher than 7:1. No addition products derived from α-anomeric aromatic imines were formed. Aliphatic homoallylamines **20** were synthesized by using allyltributylstannane in the presence of $SnCl_4$. Both *α*- and *β*-anomeric aliphatic imines reacted with the allylstannane. They gave the same ratio of diastereomers and showed the same sense of asymmetric induction.

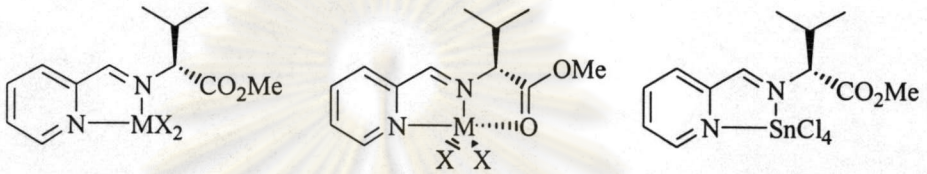


19 **20** **21**

R=Ph (**21a**); 65 % yield, *dr* = 14:1
R=3-pyridyl (**21b**); 28 % yield, *dr* = 11:1
R=*n*-C_3H_7 (**21c**); 32 % yield, *dr* = 24:1

Scheme 1.24

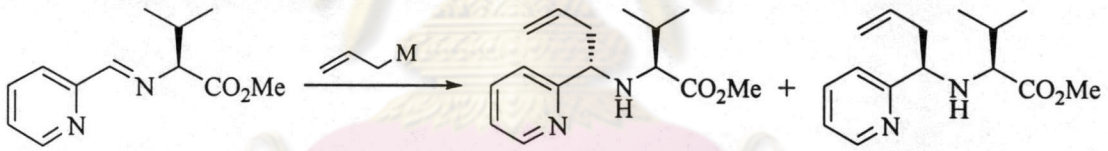
In 1996, Savois and co-workers[25] found that some allylmetal reagents (Sn, Zn) add to the imine derived from 2-pyridine carboxaldehyde and methyl (*S*)-valinate or to preformed imine-metal salt complexes (*S*)-**22** to give mainly the (*S,S*)- or the (*R,S*)-secondary homoallylic amine, depending on the nature of the allylmetal reagent. Since the imine can act as a bidentate (N,N or N,O) or tridentate (N,N,O) (**Figure 1.2**), different selectively might be achieved by varying the reagents, affording either the (*S,S*) or (*R,S*) homoallylic amines **23** (**Table 1.1**).



(*S*)-**22**-$ZnBr_2$ or -$SnCl_2$ (*S*)-**22**-$SnCl_4$

Figure 1.2 The conformations of metal salt complexes of (*S*)-**22**

Table 1.1 Preparation of secondary homoallylic amines **23** from (*S*)-**22**



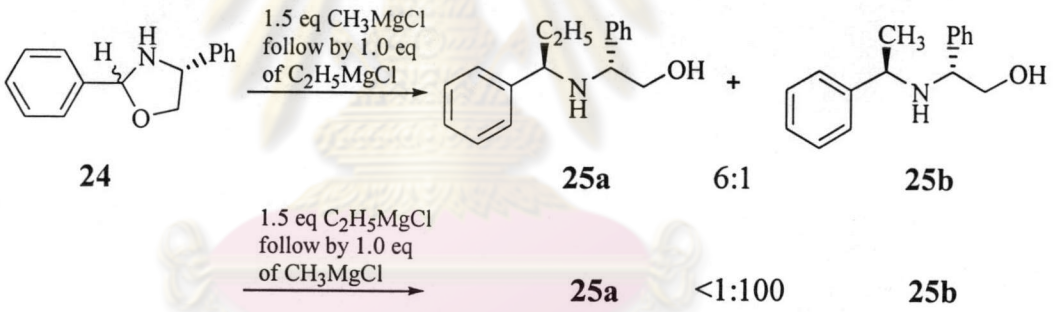
(*S*)-**22** (*S,S*)-**23** (*R,S*)-**23**

Entry	Reagents (eq.)	T (°C)	Yield (%)	(*S,S* : *R,S*)
1	Allyl-ZnBr (2)[a]	-78	98	86:14
2	Allyl-Br (1.1), Zn (1.5)[b]	25	75	80:20
3	Allyl-$SnCl_3$ (1)[a]	-78	100	13:87
4	Allyl-I (1.5), $SnCl_2$ (1.1)[b]	25	100	4:96
5	Allyl-MgCl (1.1)[a]	-78	70	83:17
6	Allyl-MgCl (1), $SnCl_4$ (1)[c]	-78	80	65:35

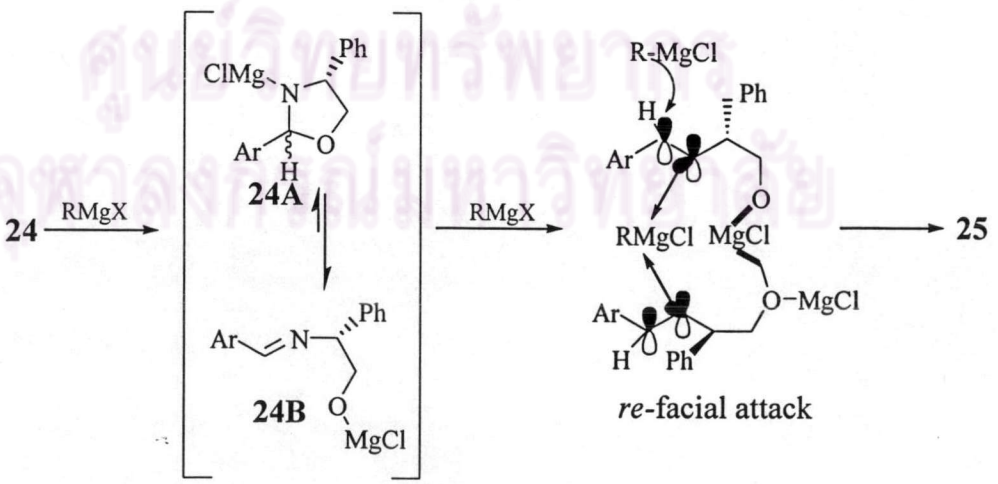
[a]The imine was added to the allylmetal.
[b]The allyl halide was added dropwise to the mixture of the imine and the other reagent(s).
[c]The salt was added to the imine at 25 °C and the mixture was stirred for 10 min, then cooled to –78 °C, and the allylmetal was added.

In 1991, Wu and Pridgen[26] reported Grignard addition to oxazolidine derived from (*R*)- and (*S*)-phenylglycinol and aldehydes. The reaction occurred readily under THF reflux (4-24 h) with very high diastereoselectivity (average ~ 96 % *de*).

At least ~1.5 eq of the organometallic reagent was required to force the reaction to completion and achieve high diastereoselectivity. In an interesting experiment, the addition of 1.5 eq of methyl Grignard to **24** followed shortly by 1.0 eq of ethyl Grignard reagent, the resulting major product was predominately derived from the addition of ethyl group rather than methyl (6:1 ratio). Reversing the order of addition led to a reversal of product selectivity, but with an even greater disparity in the ratio of products (>100:1) (**Scheme 1.25**). This unprecedented high level of asymmetric induction for Grignard addition to the normally tautomeric oxazolidine/imino functionality may be attributed to a highly ordered transition state resulting from significant chelation of the alkoxy substituent and imino nitrogen to at least one magnesium cation. The Grignard reagent then attacks the *re* face of C-2 of either **24A** or **24B** from the less hindered side, distal to the *R* substituent of the amino alcohol moiety (**Scheme 1.26**).

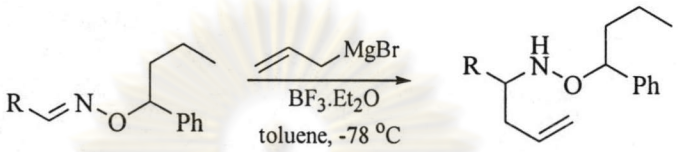


Scheme 1.25



Scheme 1.26

In 1998, Moody and Hunt[27] reported a new asymmetric synthesis of β-amino acids base on the addition of allylmagnesium bromide to a range of chiral aldoximes derived from phenylalkyl hydroxyamine (**Scheme 1.27**). The oxime ethers **26** underwent addition of allylmagnesium bromide in the presence of borontrifluoride etherate to give the hydroxylamines **27** in excellent yield and high diastereoselectivity.

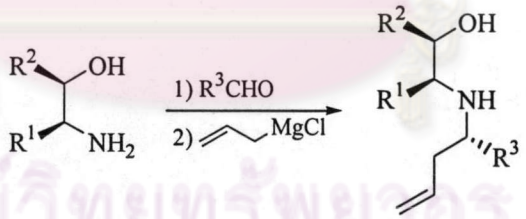


26 **27**

R = Ph; (*R*)-**27a**; 100 % yield, *92 % de*
R = 4-$MeOC_6H_4$; (*S*)-**27b**; 80 % yield, > 96 % *de*
R = ^{c}Hex; (*R*)-**27b**; 80 % yield, 96 % *de*
R = ^{i}Pr; (*R*)-**27b**; 78 % yield, 86 % *de*

Scheme 1.27

In 2000, Couty and co-worker[28] discovered a diastereoselective reaction of an allyl Grignard reagent with the product resulting from the condensation between an enantiopure β-amino alcohol **28** and an aldehyde (**Scheme 1.28**).

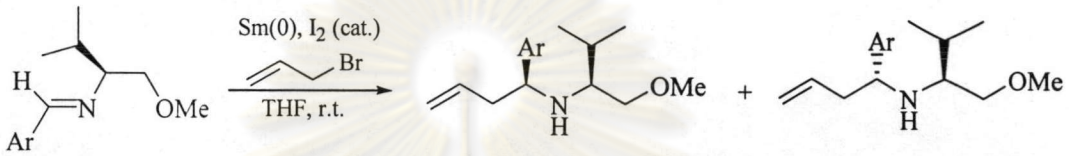


28 **29**

Scheme 1.28

Two enantiopure β-amino alcohols, namely (1*R*,2*S*)-norephedrine (**28**: R^1 = Me, R^2 = Ph) and (*S*)-phenylglycinol (**28**: R^1 = Ph, R^2 = H) were used as chiral sources and were condensed with various aldehydes (R^3 = Ph, *n*-C_9H_{20}, (*E*)-CH=CHPh). Allylation was effected on the crude condensation product using 3 eq of allylmagnesium chloride in THF. The procedure gave homoallylic amines in fair to good yield (50-75 %) with diastereomeric ratio of 80-95 % as determined by ^{1}H-NMR.

The chemistry involving the use of samarium (II) compounds is difficult due to their sensitivity to air. In 1999, Yanada and co-worker[29] have studied the direct use of metallic Sm to improve on this shortcoming of SmI_2. Barbier-type allylation of optically active imine such as *N*-benzylidenevalinol methyl ether was performed with metallic samarium, a catalytic amount of iodine, and an allyl halide. This reaction proceeded in a highly diastereoselective manner in THF at room temperature (**Scheme 1.29**).

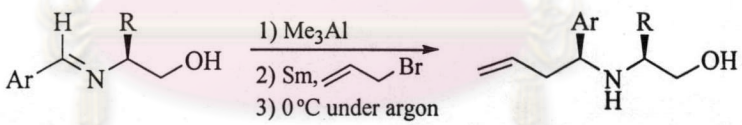


30 **31** **32**

Ar = 4-MeO-C_6H_4, 93 % yield, **31:32** = 97:3
Ar = 2-MeO-C_6H_4, 77 % yield, **31:32** = 99:1

Scheme 1.29

In 2001, Yanada[30] reported stereoselective radical reactions of optically active imines bearing a *β*-hydroxy group with metallic samarium (Sm) after treating of the imines with trimethylaluminum (**Scheme 1.30**).

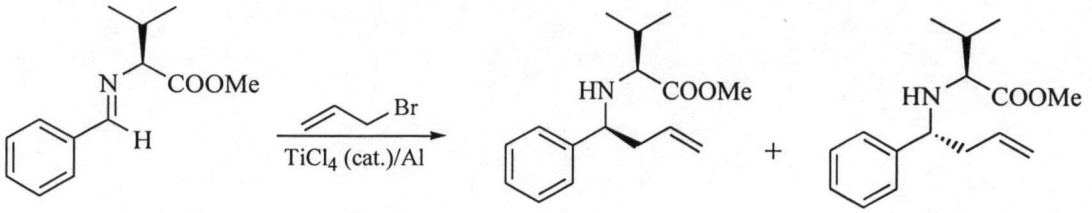


33 **34**

34a Ar = Ph, R = (*S*)-^{i}Pr, 96 % yield, *dr* > 99:1
34b Ar = *p*-Tol, R = (*S*)-^{i}Pr, 94 % yield, *dr* > 99:1
34c Ar = Ph, R = (*R*)-Ph, 93 % yield, *dr* > 99:1
34d Ar = *trans*-PhCH=CH-, R = (*S*)-^{i}Pr, 70 % yield, *dr* > 99:1

Scheme 1.30

Torii[31] and co-workers reported the Barbier Type allylation of imines with allyl bromide by the action of aluminum (1 eq) and titanium(IV) chloride (0.05 eq) in THF (**Scheme 1.31**). Chirality transfer of *L*-valine to homoallyl amine can be achieved successfully by the $TiCl_4$ (cat.)/Al-promoted allylation of *N*-benzylidene-*L*-valine methyl ester followed by alkaline hydrolysis and electrolytic decarboxylation. This afforded a 20:1 mixture of the adducts (*S*,*S*) and (*S*,*R*) in 81 % yield.



Scheme 1.31

The stereochemical outcome observed might be explained by assuming the following acyclic transition state model (**Figure 1.3**).

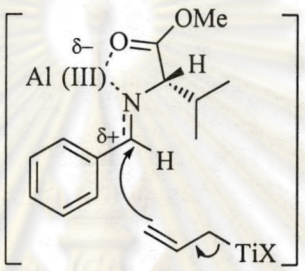
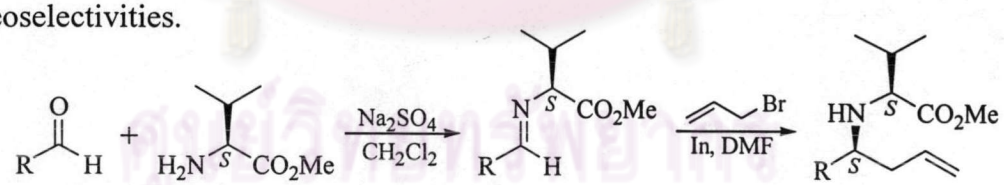


Figure 1.3 A cyclic transition state model

In 1997, Loh and co-workers[33] presented the indium-mediated allylation of one-pot imine reaction derived from L-valine methyl ester (**Scheme 1.31**). The stereochemistry is controlled only by direct chelation of the indium species to give the respective chiral homoallylic amines and amino acids in high yields and stereoselectivities.



R=Ph, 3-pyridyl, cyclohexyl; 75-80 % yield, *dr* = 99:1

Scheme 1.32

Loh has proposed a transition state model shown in **Figure 1.4** to explain the stereoselectivities.[33]

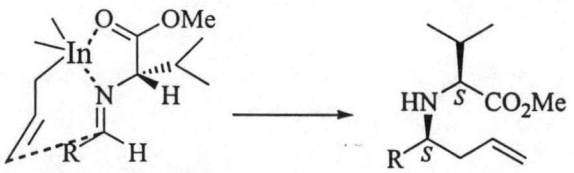
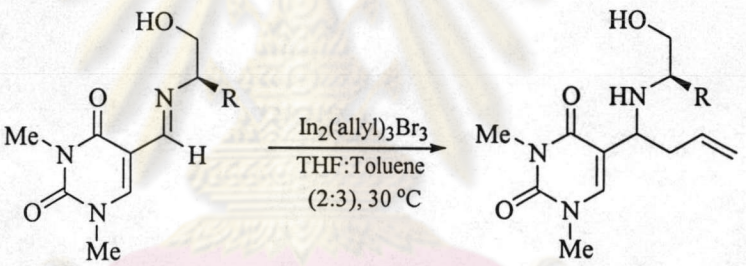


Figure 1.4 The transition state of indium species

In this model, the indium species was believed to be chelated by the nitrogen and the carbonyl group of the ester. Owing to the rigid *N*, *O*-bidentate conformation, the bulky isopropyl group of the valine chiral auxiliary selectively shields one face and hence allowing allylic delivery only to the *si* face. As a result, only the (*S,S*)-diastereomers predominate in all cases.

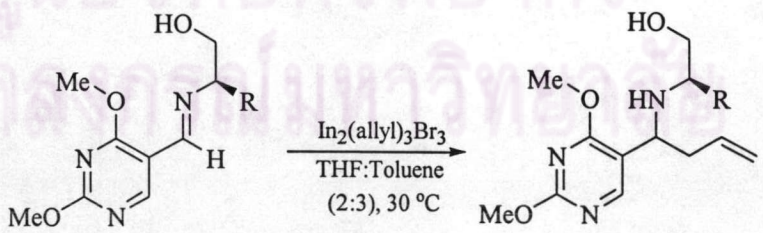
Furthermore, in 2001, Kumar and co-worker[34] presented another way to control the diastereoselective synthesis of homoallylic amine by C-4 carbonyl of uracil (**Scheme 1.33**). They reported a 5-formyluracil derivatives and their Schiff bases with chiral amino alcohols undergo highly diastereoselective 1,2- and 1,3-allylations. The absence of the C-4 carbonyl in the case of 2,4-dimethoxy-5-formylpyrimidine and its Schiff bases leads to complete loss of diastereoselectivity. The allylations of the Schiff bases were carried out by first forming the $In_2(allyl)_3Br_3$ reagent in THF-toluene (2:3).



35 **36**

36a R = Ph, 62 % yield, *dr* > 98:2
36b R = CH_2Ph, 66 % yield, *dr* > 96:4
36c R = ^{i}Pr, 68 % yield, *dr* > 98:2

Scheme 1.33



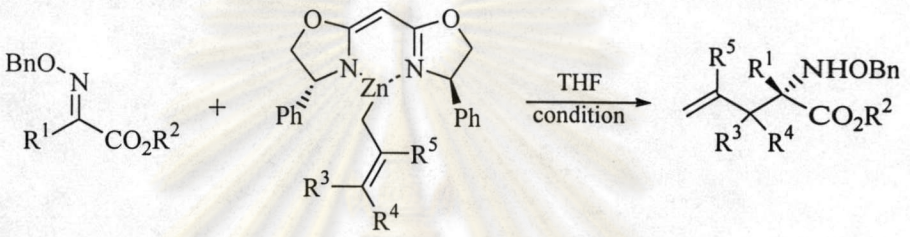
37 **38**

38a R = Ph, 66 % yield, *dr* > 1:1
38b R = CH_2Ph, 68 % yield, *dr* > 1:1
38c R = ^{i}Pr, 68 % yield, *dr* > 2:1

Scheme 1.34

All asymmetric allylations described above belong to the second generation asymmetric synthesis. Only a few third and fourth generation examples have been reported so far, of which some representative ones will be discussed.

Hanessian and Yang[32] described a highly enantioselective allylation of oximes of α-ketoesters with phenyl substituted chiral bis(oxazoline) **40** as external ligand of allylzinc reagents (**Scheme 1.35**). This method provides an efficient and convenient access to *N*-benzyloxy allylglycine, allylglycine and chain-substituted variants with high enantiomeric purities (62-90 % yield, 74-94 % *ee*) (**Scheme 1.35**).



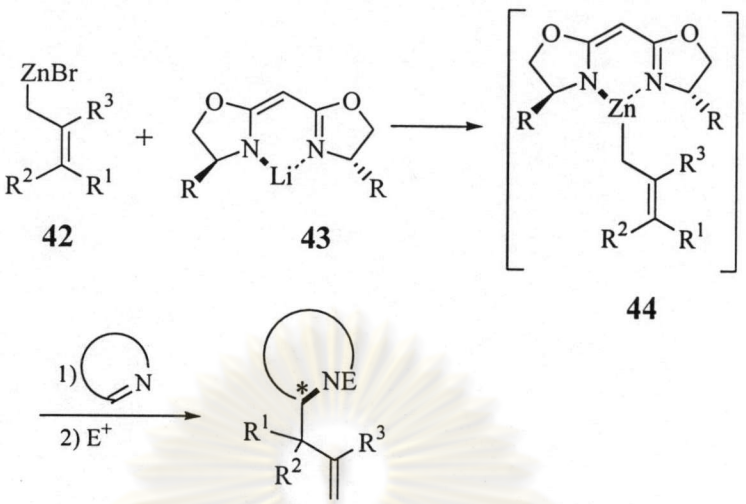
39 **40** **41**

a R^1 = H, R^2 = ^{i}Pr
b R^1 = H, R^2 = ^{t}Bu
c R^1 = Me, R^2 = Et

a R^3 = R^4 = R^5 = H
b R^3 = R^4 = H, R^5 = Me
c R^3 = R^4 = H, R^5 = Ph
d R^3 = R^4 = H, R^5 = CO_2 ^{t}Bu
e R^3 = R^4 = Me, R^5 = H

Scheme 1.35

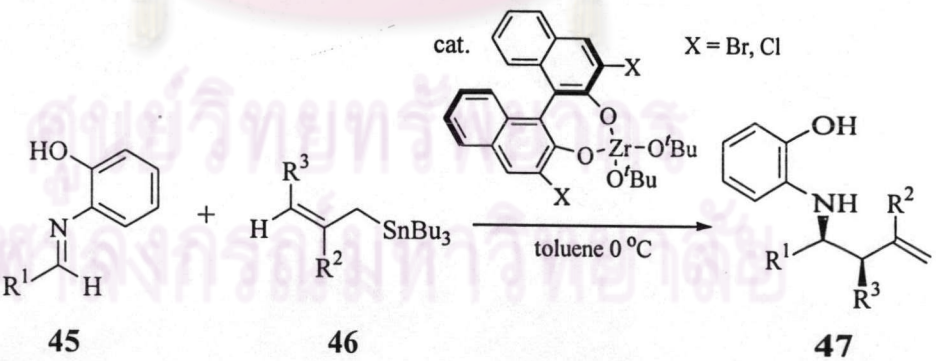
In 1996, Nakamura and co-worker[43] found that the presence of a lithiated bis-oxazoline ligand (**43**), an allylic zinc reagent (**42**) reacts with a cyclic aldimine to give an allylated secondary amine with enantioselectivity of 88-99 % *ee* (**Scheme 1.36**).



a: $R^1 = R^2 = R^3 = H$; **b**: $R^1 = R^2 = H$, $R^3 = Me$;
c: $R^1 = R^2 = H$, $R^3 = SiMe_2Ph$; **d**: $R^1 = Ph$, $R^2 = R^3 = H$
$E^+ = MeOH, (CF_3CO)_2$
$E = H, COCF_3$ or Ts

Scheme 1.36

In 2001, Kobayashi and co-worker[44] reported the chiral Lewis acid catalysts that are suitable for the activation of bidentate imino compounds. The viability of this approach is illustrated by the allyltion of imines **45** with allylstannanes **46** to afford the corresponding homoallylic amines **47** in good yields (74-91 %) and with high stereoselectivities (54-83 % *ee*) (**Scheme 1.37**).



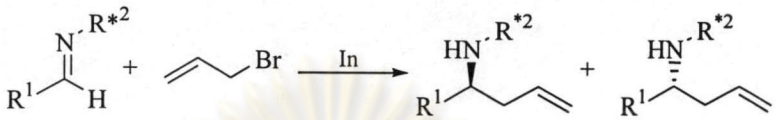
45a: $R^1 = Ph$
45b: 1-naphthyl
45c: $3,4\text{-}(OCH_2O)C_6H_3$
45d: $2,3\text{-}(MeO)_2C_6H_3$
45e: 2-furyl
45f: $p\text{-}ClC_6H_4$

46a: $R^2 = CH_3$, $R^3 = H$
46b: $R^2 = CH_2OTBS$, $R^3 = H$
46c: $R^2 = CH_2OH$, $R^3 = H$
46d: $R^2 = CH_2OH$, $R^3 = CH_3$

Scheme 1.37

1.4 Objectives of this research

The objectives of this research were to develop nucleophilic addition of carbon nucleophiles to chiral imines. The carbon nucleophile used in this study is an allylindium reagent formed *in situ* from an allyl bromide and indium metal.



Scheme 1.38

Interestingly, while indium-mediated allylation of sulfonimine[25] and hydrazones[26] in aqueous or protic medium is well established, the analogous allylation of imines are invariably accomplished in aprotic solvents such as THF and DMF under anhydrous conditions. It is interesting to investigate the optimum condition of allylation of imines by using organoindium reagent in aqueous or protic solvents and to apply this condition to asymmetric synthesis. Furthermore, factors affecting the chiral auxiliary efficiency including type of amines, solvents and temperature will be explored. Two of the most important parameters to be considered whether or not the reaction is successful are yield and enantiomeric purity of the products. Diastereoselectivity could be expressed in term of % *ds* which is defined as the percent ratio of the respective diastereomers. The ratio of diastereomers can be conveniently measured by NMR spectroscopy.