Organometallic Reactions in Aqueous Media: Reactivity, Selectivity and Synthetic Applications

A thesis submitted to the Faculty of Graduate Studies
and Research in partial fulfillment of the requirements
of the degree of

Doctor of Philosophy

By

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To the loving memory of my Grandma, Lu Ruiting,

for her deep unselfish love.

献给我亲爱的奶奶，卢瑞亭，

感谢她一生对我无私的关爱。

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Abstract

Because of the concern for the environment and the search for the synthetic efficiency, the metal-mediated aqueous carbon-carbon bond formation reactions were studied. By employing sulfonimines, the scope of the metal-mediated aqueous Barbier-type allylation reactions was expanded to C=N electrophiles and the regio- and stereoselectivities of these reactions were examined.

The stereochemical factors in the indium-mediated aqueous Barbier-type allylation reactions of sulfonimines were investigated, and chelation control was observed and applied in the stereoselective crotylation reactions. By using chiral-modified sulfonimines or sulfinimines, the asymmetric aqueous Barbier-type allylation reaction of C=N electrophiles was also studied.

Highly regioselective propargylation reactions of sulfonimines mediated by zinc were discovered through the coupling of propargylic bromides with sulfonimines in aqueous media. Beyond the allylation transformations, zinc was also found as the metal of choice for the mediation of the Barbier-type benzylation reaction of sulfonimines and the coupling reaction of aldehydes with α-bromoacetonitriles in aqueous media.

The indium-mediated aqueous coupling reaction of 1, 4-dibromobut-2-yne with aldehydes was demonstrated to be a concise way for the synthesis of 1,3-dien-ol compounds. Further synthetic applications of this reaction including the intro-molecular Diels-Alder reactions were preliminarily studied.

Résumé

Du fait de leur impact sur l'environnement et de leur grande utilité en synthèse, les réactions de formation de nouvelles liaisons carbone-carbone en milieu acqueux par les métaux ont été étudiées. L'utilisation des sulfonimines nous a permis d'étendre ce type de réactions aux molécules contenant une double liaison C=N. La régio-, ainsi que la stéréosélectivité de ces réactions ont été examinées.

La stéréochimie des réactions d'allylation de type Barbier des sulfonimines par l'indium ont été étudiées. Un contrôle de la stéréochimie par chélation a été mis en évidence, et appliqué à la synthèse de réactions de crotylation hautement stéréosélectives. L'utilisation de sulfonimines, ou des sulfinimines chirales a aussi été largement étudiée lors des réactions asymétriques d'allylation de type Barbier.

Les réactions hautements régiosélectives de propargylation des sulfonimines par le zinc ont été mises au point lors de l'étude de réactions de couplage des bromures propargyliques avec des sulfonimines en milieu aqueux. Au travers de ces transformations, nous avons montré que le zinc était un métal de choix pour les réactions de benzylation de type Barbier des sulfonimines, ainsi que pour les réactions de couplage des aldéhydes avec des bromoacétonitriles en milieu acqueux.

Nous avons aussi montré au cours de ce travail que la réaction de couplage par l'indium en milieu acqueux du 1,4-dibromobut-2-yne avec divers aldéhydes nous permettait de préparer des composés bifonctionnalisés de type 1,3-dien-ols. D'autres applications synthétiques concernant cette réaction, incluant des réactions intramoléculaires de Diels Alder sont présentement en cours d'études.

List of Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
br	broad spectral signal
Bu	butyl
Bz	benzoyl
cat.	catalyst
CI	chemical ionization
Cp	cyclopentadienyl
δ	chemical shift
d	doublet
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCB	2',6'-dichlorobenzyl
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DMA	*N,N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide

DTAD	di-*tert*-butyl azodicarboxylate
EI	electron impact
eq.	equivalent
Et	ethyl
FAB	fast atom bombardment
hr	hour
Hz	hertz
IMDA	intra-molecular Diels-Alder reaction
IR	infra-red spectroscopy
KDN	3-deoxy-D-glycero-D-galacto-nonulosonic acid
LHMDS	lithium hexamethyldisilazide
liq.	liquid
HRMS	high resolution mass spectroscopy
m	multiplet
Me	methyl
MOM	methoxylmethyl
mp	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
Piv	pivaloyl
Pr	propyl
py	pyridine

q	quartet
rt	room temperature
s	singlet
SET	single electron transfer
SM	starting material
SW	supercritical water
t	tert or triplet
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	toluenesulfonyl

Chapter 1

Introduction

1.1 Organic Reactions in Unconventional Media. An Overview

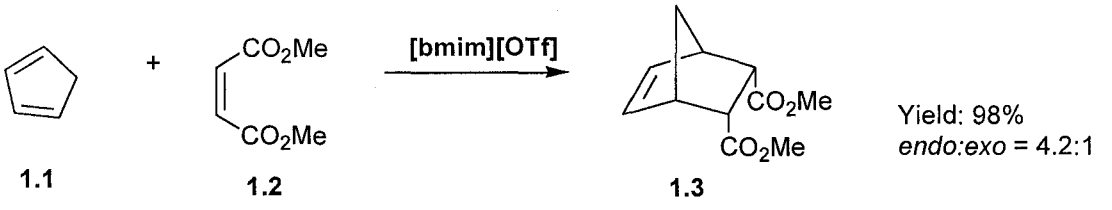
Recently, organic chemistry has witnessed some dramatic changes in the use of reaction media. The impetus of this change is from the emerging requirements on organic synthesis such as atom efficiency and environmental concerns. The following is a brief review of unconventional reaction media developed in recent years.

Water and Aqueous System:[1] Despite the fact that water is the cheapest, safest and most available solvent on our planet, chemists have only recently come to appreciate the enormous potential that water holds, in part because of water's unique enthalpy and entropy properties. First noted in Diels-Alder[2] and other pericyclic reactions,[3] water has begun to show its unique role as reaction media in organic synthesis. One recent progress is the discovery of new organoindium chemistry leading to the exploration of performing organometallic reactions in aqueous media.[4] A detailed account of this progress will be given in the later part of this chapter.

Ionic Liquids[5]: Ionic liquids are low melting organic salts that are liquids at ambient temperature. The advantages of using ionic liquids as reaction media can be attributed as follows: 1. They are good solvents for a wide range of both inorganic and organic

materials. 2. They are often composed of poorly coordinating ions, so they have the potential to be highly polar yet non-coordinating solvents. 3. They are immiscible with a number of organic solvents in forming two-phase systems. 4. Ionic liquids are nonvolatile.

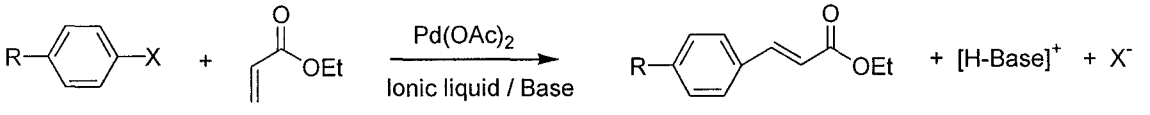
With their low volatility and ease of recycling, ionic liquids can act both as a solvent and as a catalyst depending on their Lewis acidities and other properties. The use of ionic liquid in organic synthesis is still at its early stage. The discovery of their applications in reactions such as the Friedel-Crafts reactions, the Diels-Alder reaction (Scheme 1.1) and the Heck reaction (Scheme 1.2), leads to the increasing interest of using this novel media for synthesis. [6]



1.1 1.2 1.3

[bmim][OTf]: 1-butyl-3-methylimidazolium trifluoromethanesulfonate

Scheme 1.1

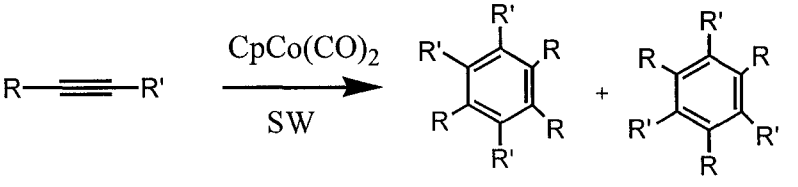


1.4 1.5 1.6 R=H, OMe; X=Br, I

Scheme 1.2

Supercritical Fluids[7]: Driven by the search for "green" or environmentally benign chemical processes, water and other fluids near or above their critical points, are also attracting increasing attention as media for organic synthesis. The ability to fine-tune the solubility properties of supercritical fluids makes them useful in a variety of applications in organic synthesis. Another important advantage of supercritical fluids is the ease of

solvent removal by simply reducing the pressure of the reaction system. Supercritical carbon dioxide has been successfully applied in a variety of reactions such as the Diels-Alder reaction, enzyme-catalyzed reactions, and asymmetric hydrogenation.[8] On the other hand, supercritical water (SW) has also been used. SW at the critical temperature of 374 °C and the critical pressure of 218 atm has a moderate dielectric constant (ε_C=5). Many nonpolar organic molecules become soluble in SW. Many studies had been conducted on organic transformation including the Heck[9] and Diels-Alder reactions in SW.[10] Parsons[11] *et al.* reported that alkynes can undergo cyclotrimerization in SW when catalyzed by $CpCo(CO)_2$. (Scheme 1.3)



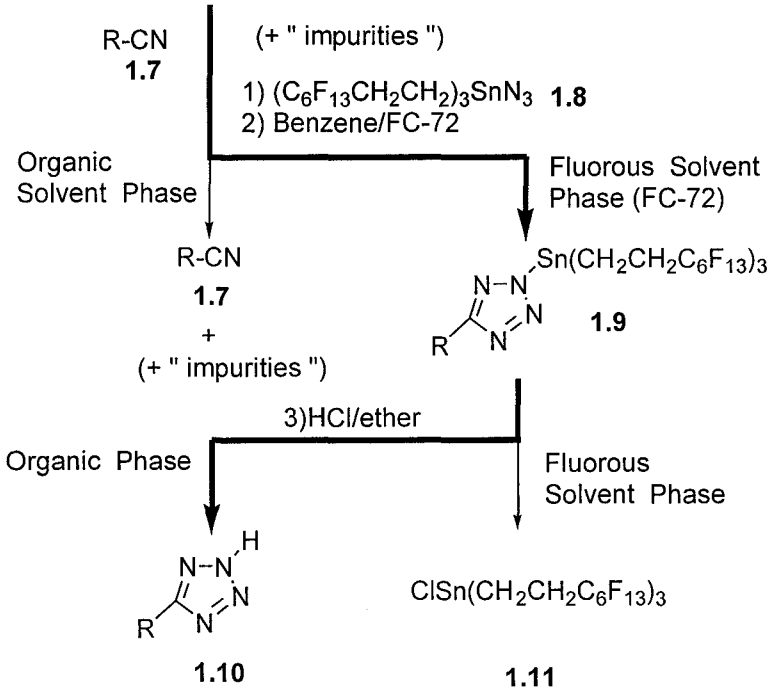
R=$CH_3(CH_2)_2CH_2$, C_6H_5, CH_3
R'=H, CH_3

Scheme 1.3

Derivatized and Immobilized Solvents: Derivatized solvents are modified solvent molecules that are designed to mimic the solubility properties of the original solvents while greatly reducing their volatility. Immobilized solvents may be solvent molecules that are tethered to a low molecular-weigh polymer, thus reducing its volatility.

The use of derivatized solvents is still at the early stages of development. The potential applications extend however beyond synthesis to purification and separation process.[12] Recently, a "fluorous synthesis" approach had been developed in which organic molecules are rendered soluble in fluorocarbon solvents by attachment of a

suitable fluorocarbon group. Fluorocarbon solvents are usually immiscible in organic solutions, and fluorous molecules partition out of an organic phase and into fluorous phase in a standard liquid-liquid extraction. A remarkable example for this application in organic synthesis was reported by Curran[13] *et al.* A fluorous-phase strategy was developed successfully in nitrile oxide cycloaddition. Reaction of nitrile **1.7** in two-fold excess with fluorous-labled azide **1.8** in BTF (benzotrifluoride) at 80 °C for 12 hr provided the fluorous tetrazoles **1.9** in high yield. After organic and fluorous extraction (benzene and FC-72, a mixture of perfluorohexanes, C_6F_{14}, bp 56 °C), the unreacted nitrile and impurities were easily removed. After brief exposure of the product **1.9** to ethereal HCl, followed by organic and fluorous extraction (acetonitrile and FC-72), evaporation of the acetonitrile phase provided the pure tetrazoles **1.10**. (Scheme 1.4) The example shows that the fluorous-phase switch can provide pure organic products even in reactions that do not occur in quantitative yield, and can be used to remove fluorous reagents and by-products from organic products.



Scheme 1.4

1.2 The New Role of Water in Organic Synthesis.

Despite the fact that water is the most easily available solvent, the use of water as solvent for organic synthesis was a fairly rare occurrence in organic chemistry. In the recent two decades, the discovery of new potentials that water holds in organic chemistry has invoked extensive investigations of using water for organic synthesis. The interest of using aqueous media in synthesis can be attributed to the following concerns in modern organic synthesis.

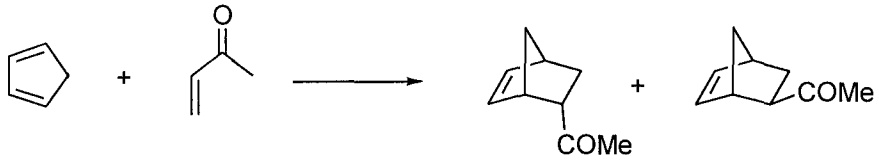
1.2.1 Green Chemistry

"Green Chemistry is carrying out chemical activities—including chemical design, manufacture, use, and disposal—such that hazardous substances will not be generated."[14] This is a very simple yet global view of how the field of chemistry should be perceived and practiced. Just as chemists are needed to fully understand the nature and source of environmental problems that result from certain chemicals released to the environment, chemists are also required to use that understanding in preventing the problems from occurring in the first place. In organic reactions, many solvents used have been found to possess serious toxic or otherwise hazardous properties. Halogenated solvents such as carbon tetrachloride, perchloroethylene, and chloroform, for example, have been implicated as potential and/or suspect carcinogens. Chlorofluorocarbons (CFCs), used in high volumes as refrigerants and in other applications, were recently banned for their role in stratospheric ozone depletion. To avoid the hazardous properties of organic solvents, extensive studies on water as alternative solvent have been conducted since 1980. Water

is the most abundant solvent in nature and is the basis and bearer of life. By using water, the burden of organic solvent disposal in industry can be reduced. That is consistent with pursuing of the goals of Green Chemistry.

1.2.2 The Acceleration Effect of Water in Organic Reactions

Although during the preceding decades, water as solvent was, for the most part, not commonly used in organic chemistry, the fact remains that nearly all chemical reactions in life are performed in aqueous media. The discovery alerting chemists to the new role of water should be attributed to the pioneering work of the Breslow's group in the early eighties. They observed a striking acceleration effect and increased stereoselectivity by using water as solvent in the Diels-Alder reaction.[2] In their study, the acceleration effect of water on the reaction of cyclopentadiene with butenone was carefully investigated. (Scheme 1.5)



kinetics

solvent	$10^5 k_2 (M^{-1}s^{-1})$
Isooctane	5.94
MeOH	75.5
H_2O	4400
H_2O+4.86M LiCl	10800
H_2O+ 4.86M $(NH_2)_3CCl$	4300
β-cyclodextrin (10mM)	10900
α-cyclodextrin (10mM)	2610

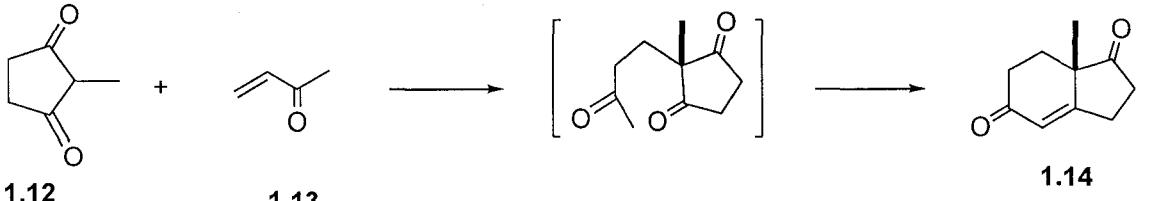
selectivity

solvent	*endo/exo*
cyclopentadiene	3.85
EtOH	8.5
0.15M CpH in H_2O	21.4
0.007M CpH in H_2O	22.5

Scheme 1.5

It has also been established that the solvent polarity was not the cause either of the selectivity or the rate enhancement in the reaction since polar organic solvents such as

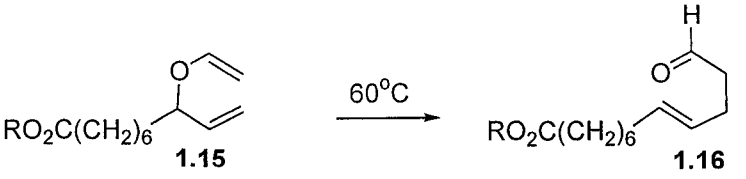
DMF or DMA did not promote the same effects. Instead, hydrophobic effect[15] was used to account for the role of water on its impact on the reaction. The hydrophobic effect is the tendency of apolar groups to aggregate in aqueous solutions, in order to minimize unfavorable interactions with water. In addition to the Diels-Alder reactions, the implication of the hydrophobic effect can also be helpful in the understanding of the acceleration of the Michael-type additions and the Claisen rearrangement. In 1970s, Hajos[16] and Wiechert[17] independently reported that the Michael addition of 2-methylcyclopentane-1,3-dione to vinyl ketone in water gave the corresponding conjugated addition product without the use of basic catalyst (Scheme 1.6). The use of water as solvent was superior both in yield and in purity of the product in comparison with the same reaction in methanol with base. Grieco[18] *et al.* reported that for the rearrangement of allyl vinyl ether carboxylate salts **1.15**, the reaction occurred 23 times faster in water than in methanol at 60 °C. (Scheme 1.7)



1.12 **1.13** **1.14**

	Yield
H_2O/no base	87.6%
MeOH/KOH	54%

Scheme 1.6



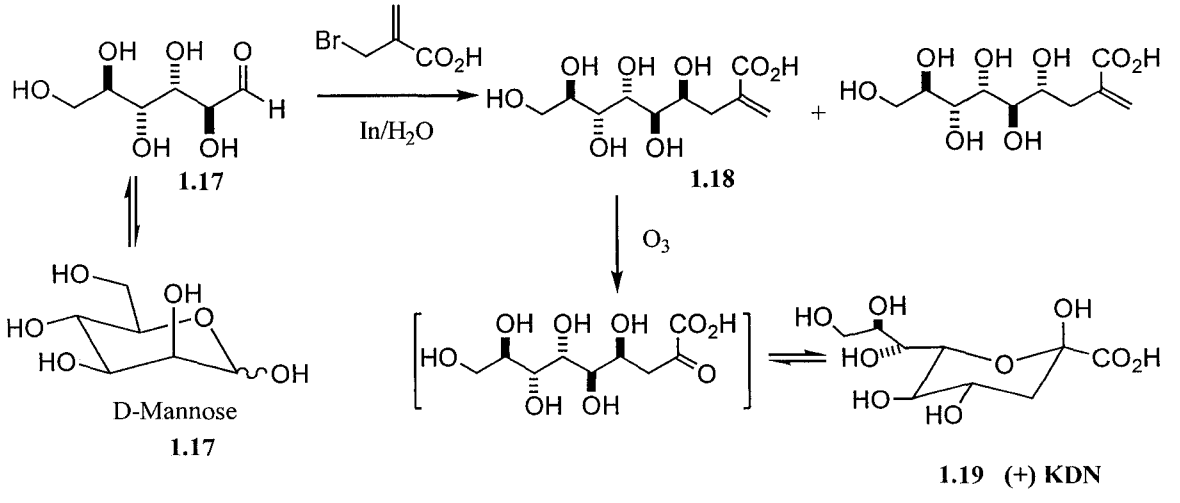
1.15 **1.16**

R	solvent	relative rate
Na	H_2O	18
Na	MeOH	0.79
Me	C_6H_6	0.17

Scheme 1.7

1.2.3 Synthetic Efficiency

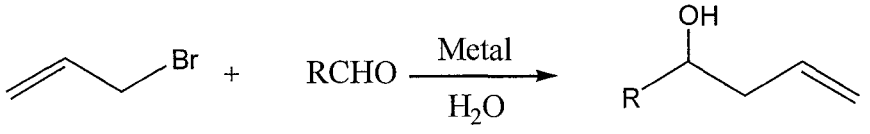
Beside environmental concerns, synthetic efficiency is another consideration in this chemistry. Synthetic efficiency cannot only be addressed in terms of selectivity (chemo-, regio-, diastereo-, and enantioselectivity) alone, but in atom economy as well, that is, maximizing the number of atoms of all raw materials that end up in the product.[19] Enhancing the efficiency in the synthesis of complex organic products constitutes one of the most exciting challenges to synthetic chemists. One way to gain synthetic efficiency is to reduce the need of protecting group chemistry. In this respect, aqueous chemistry offers considerable advantages. One of the most important features of carrying out organic reactions in water is that many reactive functional groups, such as hydroxyl and carboxylic functions, do not require the protection-deprotection protocol in such reactions. Therefore, many water-soluble compounds, such as carbohydrates, do not need to be converted into their derivatives and can be reacted directly in a synthetically efficient manner. This point has been well demonstrated in a concise synthesis of KDN, which has been developed through the use of aqueous indium chemistry. (Scheme 1.8) Starting directly from D-mannose, the tedious protection and deprotection normally required for carbohydrate chemistry were totally avoided in the synthesis.[20]



Scheme 1.8

1.3. Organometallic Reactions in Aqueous Media. The Intriguing Challenge

Since the discovery in 1849 of the formation of alkylzinc compounds by Frankland,[21] organometallic chemistry has become one of the most important parts of organic chemistry. Fruitfully and extensively explored for more than one and half centuries, organometallic reagents for synthetic purpose can be found in almost every modern organic synthesis. However, most of the organometallic reagents are notorious for their sensitivity towards moisture and are usually prepared and handled under anhydrous conditions. It had become, more or less, an article of faith for organic chemists that water should always be excluded from organometallic reactions except in rare cases.[22] This conceptual hurdle was slowly overcome with the recent discovery of the metal-mediated Barbier-type reactions in aqueous media. Various metals, reacting directly with allylic halides in aqueous media, can mediate the smooth coupling of allylic halides with aldehydes to give the corresponding homoallylic alcohols. (Scheme 1.9) The following metals, which will be discussed in details in the following sections, played the most important role in the progress of this development.

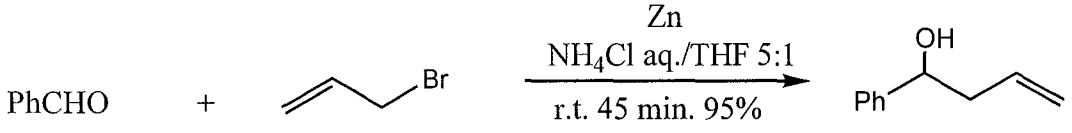


Scheme 1.9

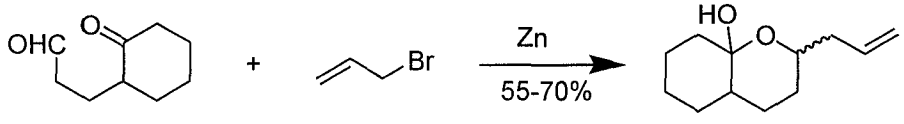
1.3.1 Zinc-Mediated Aqueous Organometallic Reactions

In aqueous media, zinc was the first metal to be used for the allylation of carbonyl compounds. In 1985, Luche *et al.* reported that zinc can mediate allylation reaction of carbonyl compounds with allyl bromide in a mixture of THF and saturated aqueous ammonium chloride solution under sonication conditions (Luche condition).[23] (Scheme

1.10) The use of NH_4Cl aq./THF solution, instead of water/THF, and the use of ultrasonic radiation, dramatically increased the yield. When a mixture of aldehyde and ketone was subjected to the reaction, highly chemo-selective allylation of the aldehyde was achieved. For example, such chemoselectivity can be illustrated in the allylation of compound **1.20** (Scheme 1.11)[24]



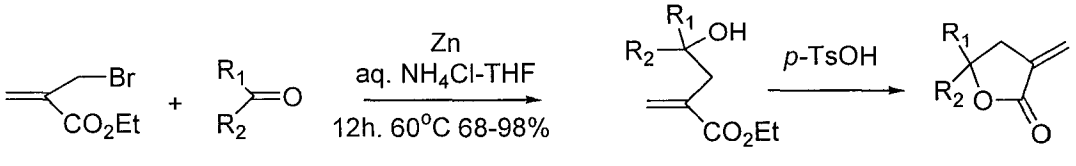
Scheme 1.10



1.20 **1.21**

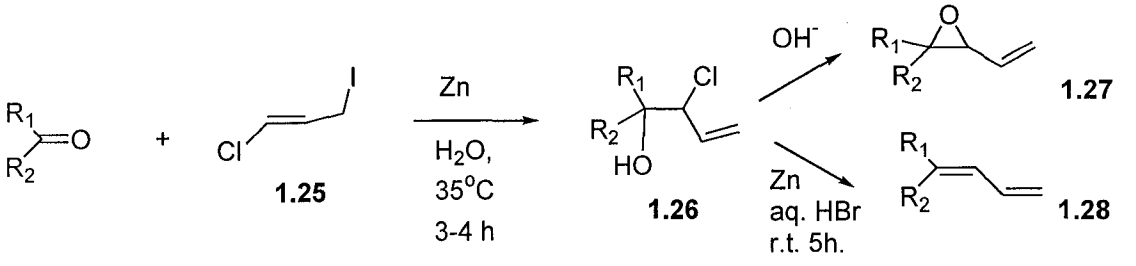
Scheme 1.11

The further investigation of this reaction involved the use of functionalized allylic bromides to examine the scope and limitation of the reaction and its synthetic implications. When ethyl (2-bromomethyl)acrylate **1.22** was used, α-methylene-γ-butyrolactones **1.24** could be obtained in good yields under reflux conditions.[25] (Scheme 1.12) Treating 1-chloro-3-iodopropene **1.25** and aldehydes or ketones with zinc powder in aqueous media also led to the corresponding chlorohydrins **1.26**, which are convenient intermediates for the preparation of vinyloxiranes **1.27** or (E)-buta-1,3-dienes **1.28**.[26] (Scheme 1.13)



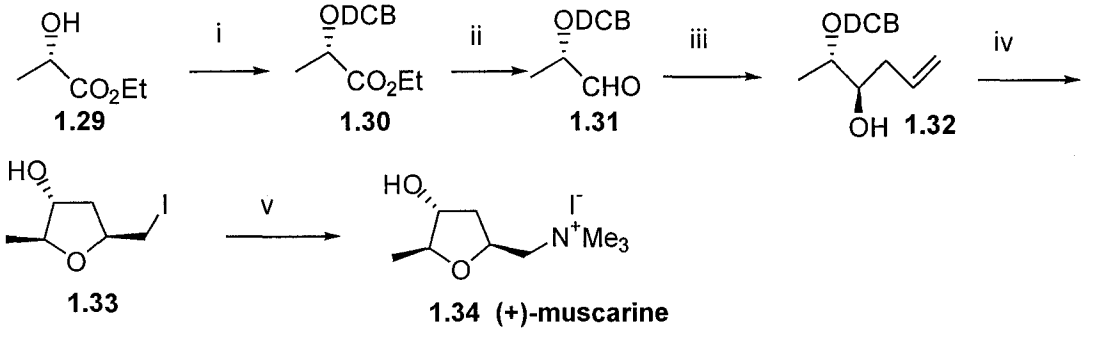
1.22 **1.23** **1.24**

Scheme 1.12



Scheme 1.13

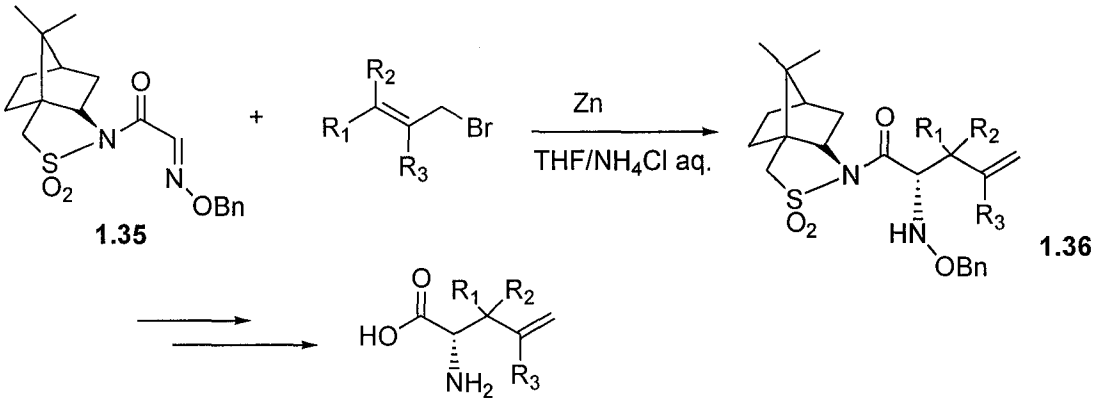
The synthetic usefulness of this reaction in organic synthesis has been demonstrated in a five-step synthesis of (+)-muscarine wherein an aldehyde **1.31** derived from ethyl (S)-lactate **1.29** was treated with allyl bromide. The strategy was based on the observation that in aqueous media, the reaction selectively gave the anti-diastereomer **1.32**.[27] (Scheme 1.14)



(i) DCBBr/Ag_2O/Et_2O, reflux, 6h (ii) DIBAL-H/Et_2O, -78°C, 2h. (iii) Allylbromide/Zn/H_2O/NH_4Cl, 3h (iv) I_2/MeCN, 0 °C, 3h. (v) NMe_3/EtOH/80 °C/4h

Scheme 1.14

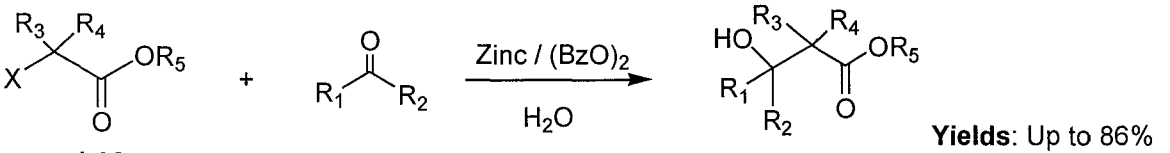
The reaction has also been successfully extended to C=N electrophiles. By the use of Oppolzer's camphorsultam as chiral auxiliary in an aqueous zinc-mediated allylation of oximes, the reaction showed diastereomeric ratios as high as 99:1. This methodology provided an efficient way for the synthesis of allylglycine and other unnatural α-amino acids.[28] (Scheme 1.15)



1.35 **1.36** **1.37**

Scheme 1.15

The zinc-mediated Reformatsky type reaction has also been realized in aqueous media by Chan's group. The reaction was limited to aromatic aldehydes and only gave moderate yields.[29] A later study reported by Bieber *et al.* showed that the yield could be improved with the aid of catalytic amount of benzoyl peroxide or peracids.[30] (Scheme 1.16)



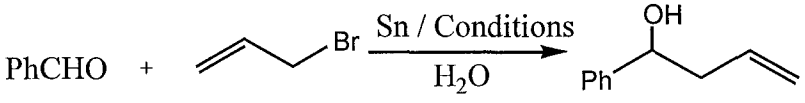
1.38 **1.39**

Scheme 1.16

1.3.2 Tin-Mediated Aqueous Organometallic Reactions

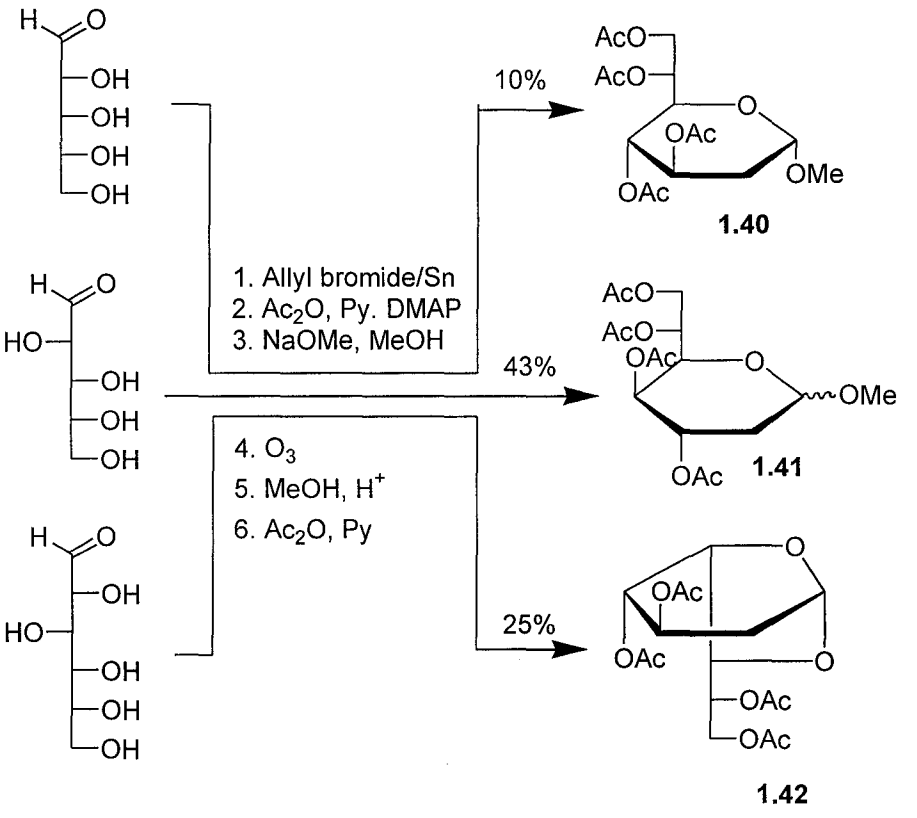
Among the metals for the Barbier-type organometallic reactions, tin offers the potential for industrial application because of its relative low cost, ready availability and relatively low toxicity.[31] Generally, activation was needed in the tin-mediated aqueous organometallic reactions. In 1983, Nokami *et al.* first reported the successful coupling of allyl bromide with carbonyl compound mediated by tin to give the homoallylic alcohol in water.[32] In that case, the reaction required catalytic amount of hydrobromic acid. Later

on, the addition of metallic aluminum powder or foil was found to improve the yield of the product dramatically.[33] On the other hand, Wu and coworkers found that higher temperature could be used to replace aluminum.[34] Alternatively, Luche found that the reaction can be performed in the absence of aluminum or hydrobromic acid by the use of ultrasonic irradiation together with saturated aqueous NH_4Cl/THF solution.[35]



Condition 1:	cat. HBr	(*Nokami et al*)
Condition 2:	cat. HCl / Al	(*Nokami et al*)
Condition 3:	heat	(*Wu et al*)
Condition 4:	NH_4Cl / ultrasound	(*Luche et al*)

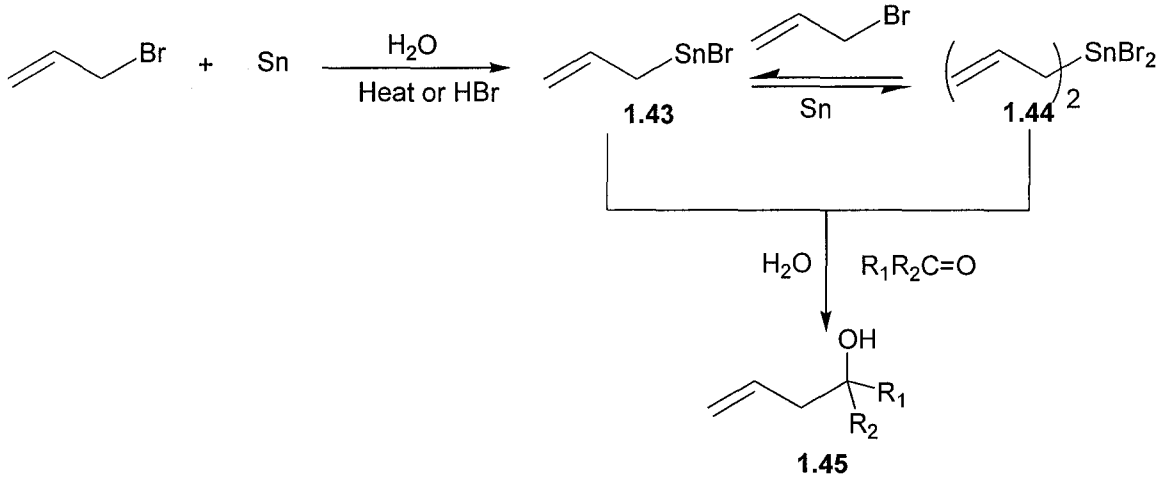
A useful application of this reaction in organic synthesis was reported by Whitesides's group.[36] Tin was used to mediate the allylation of the carbonyl function of carbohydrates in aqueous/organic solvent mixtures. The adducts were converted to higher carbohydrate homologues (**1.40** ~ **1.42**) by subsequent ozonolysis and derivatization. The reaction showed higher diastereoselectivity when there was a hydroxyl group at C-2(aldose numbering). (Scheme 1.17)



Scheme 1.17

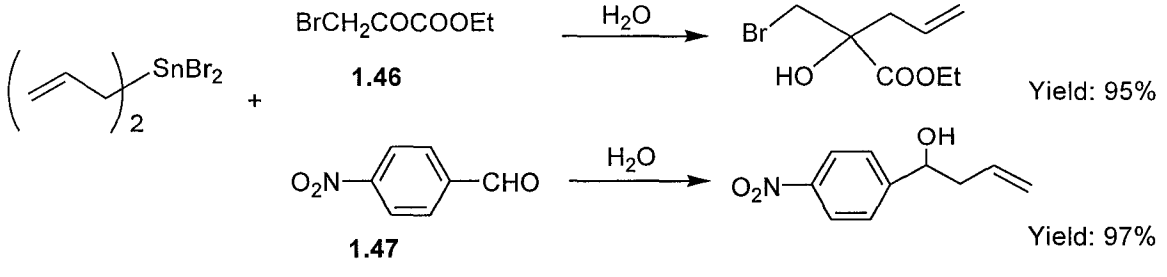
Regarding the nature of this reaction, various mechanisms have been proposed, including the intermediacy of a radical[20], radical anion[37] and an allyl metal species.[38] In the latter proposal, it was presumed that diallyltin dibromide was the organometallic intermediate in the tin-mediated allylation reactions.[39] However, no experimental proof had been offered. Recently, the nature of organotin intermediate in the aqueous tin-mediated allylation of carbonyl compounds has been elucidated.[40] It was shown that when allyl bromide reacted with tin powder in water, the first step was the formation of allyltin(II) bromide (**1.43**). This step required heating (or ultrasonic irradiation) or the use of catalyst (HBr or Al). The further conversion of allyltin(II) bromide (**1.43**) to diallyltin dibromide (**1.44**) depended on the relative amount of allyl bromide and tin in the reaction

system. Either organotin intermediates can react with carbonyl compounds to give the corresponding homallylic alcohols, while allyltin(II) bromide (**1.43**) was more reactive than diallyltin dibromide(**1.44**). (Scheme 1.18) However, these results do not eliminate the possibility of a parallel process of metal surface mediated radical or radical anion reactions.



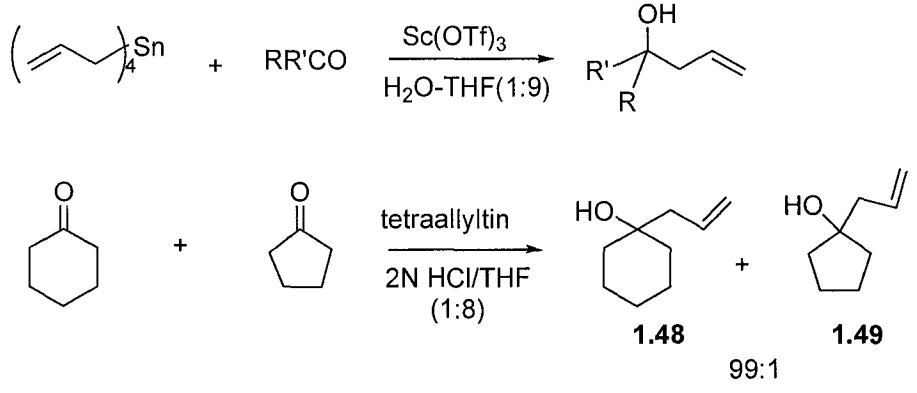
Scheme 1.18

The employment of diallyltin dibromide as an allylmetal reagent in water can overcome some problems associated with the Barbier-type conditions such as reduction and coupling reactions. For example, ethyl 3-bromo-2-oxo propionate **1.46** and p-nitrobenzaledehyde **1.47** can be allylated in water smoothly with high yields whereas the use of metallic tin will reduce the bromo- or the nitro- function. (Scheme 1.19)



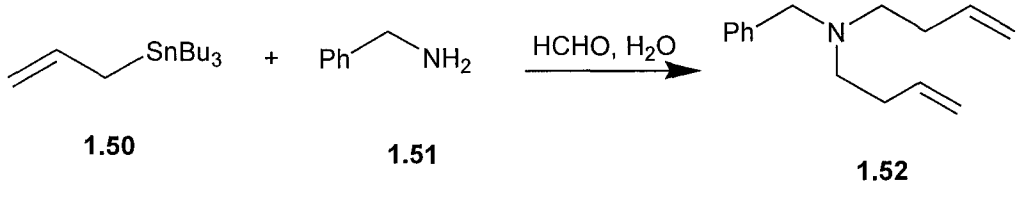
Scheme 1.19

Tetraallyltin has also been reported as an allylmetal reagent in aqueous media. The aqueous allylation reaction of carbonyl compounds can be performed smoothly either with lanthanide triflate as Lewis acid [41]or with aqueous 2N HCl/THF in a chemoselective manner.[42] (Scheme 1.20)



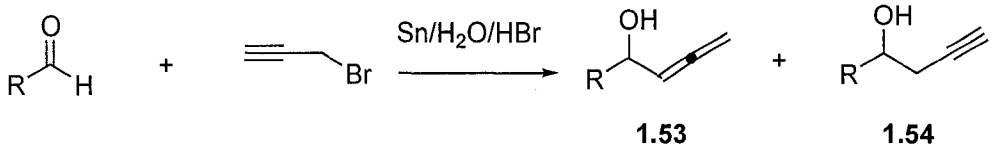
Scheme 1.20

Besides carbonyl compounds, aqueous allylation reaction can also be applied to immonium salts generated *in situ* from primary amines and formaldehyde with allylstannane **1.50**.[43] (Scheme 1.21)



Scheme 1.21

The tin-mediated aqueous organometallic reaction has also been expanded to propargyl bromide to give a mixture of allenylation (**1.53**) and propargylation (**1.54**) products. However, the reaction suffers from low regioselectivtiy for it to be synthetically useful.[44] (Scheme 1.22)

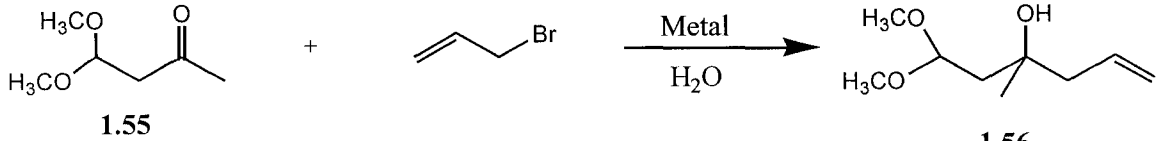


1.53 **1.54**

Scheme 1.22

1.3.3 Indium-Mediated Aqueous Organometallic Reactions

In comparison with other metals, indium has captured much of interest among the metal-mediated aqueous organometallic reactions. This is mostly because of the observation that, unlike other metals, which require activation in water, indium can smoothly mediate the coupling reaction of allylic halides with carbonyl electrophiles. The unique properties of indium have been summarized by Chan and Li.[45] **1**. Indium is unaffected by boiling water; **2**. it does not form oxides readily in the air; and **3**. its first ionization potential is low. In 1991, Chan and Li reported the first example of indium-mediated Barbier-type reactions in water.[46] The advantage of indium was demonstrated in the allylation of carbonyl compounds containing acid-labile groups. In the reaction with 4,4-dimethoxybutan-2-one (**1.55**), only indium gave the desired product in good yield. (Scheme 1.23)

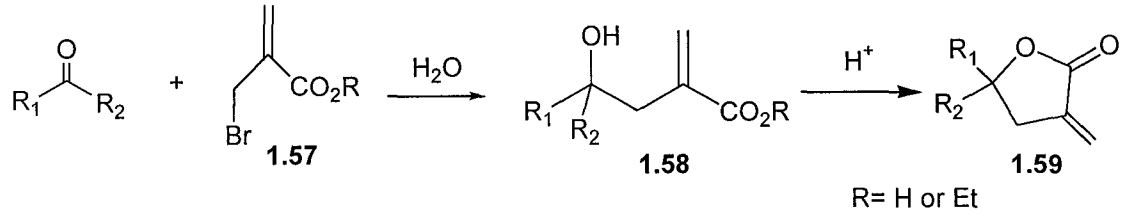


1.55 **1.56**

Metal	Yield (%)
Zn	0
Sn	10 (Under sonication)
In	70

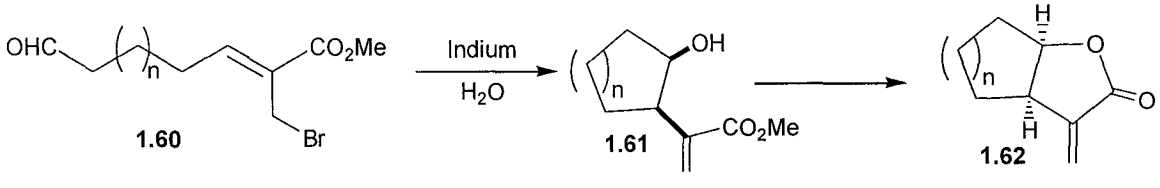
Scheme 1.23

1.3.3.1 Scope and Limitations: Although allyl bromide is the most often used, chloride and iodide can also be applied to the reactions. The reaction tolerates a variety of functional groups except the nitro function, both on the carbonyl substrates and on the allyl bromides. Such tolerance gives the reaction broad synthetic applications. For example, carboxylic acid and ester functions on the bromide are not affected by the allylation conditions and the reaction can serve as an efficient method for preparing acrylic esters and acids.[47] (Scheme 1.24)



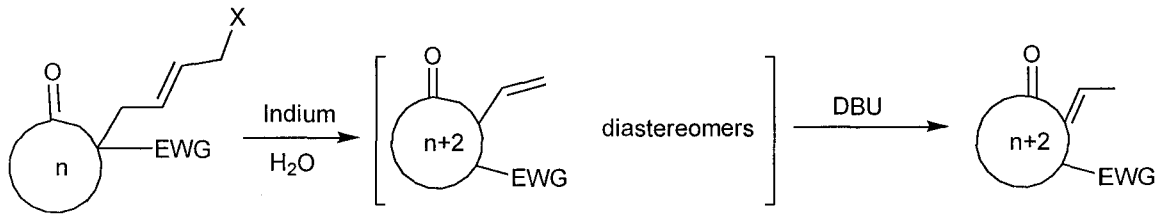
Scheme 1.24

The aqueous indium-mediated Barbier-type allylation reaction can be performed intramolecularly, as described in the carbocyclization reactions of compound **1.60** yielding 5-7-membered ring compounds **1.61**, which further cyclized to give fused α-methylene-γ-lactones **1.62**. The ring junction stereochemistry in the fused lactones was found to be *cis* in all cases.[48] (Scheme 1.25)



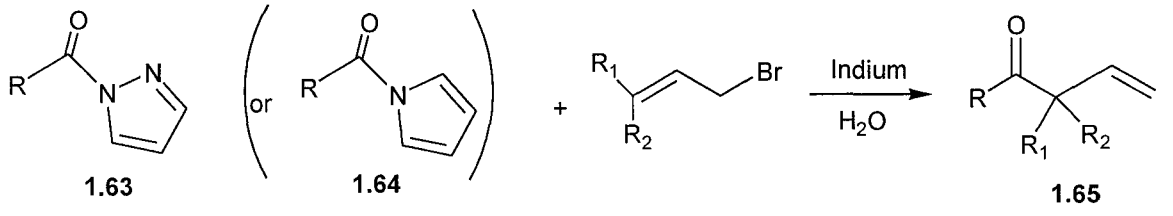
Scheme 1.25

Similar intramolecular aqueous coupling reaction led to a ring enlargement reaction reported by Li *et al.* This carbocycle enlargement reaction was applied to five- six-, seven, eight- and twelve- membered ring compounds.[49] (Scheme 1.26)

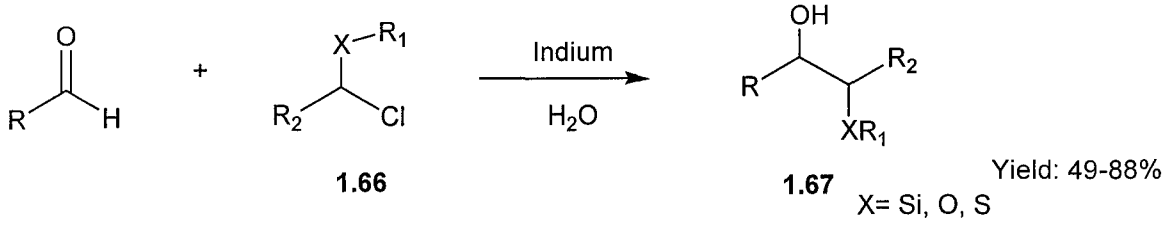


Scheme 1.26

Further effort on expanding the scope of this reaction led to the discovery of the indium-mediated allylation of other electrophiles such as acryloyl-imidazoles or pyrazoles giving β, γ-unsaturated ketone.[50] (Scheme 1.27) As another example, α-chloroheteroatomic species **1.66** (including silyl-, thio-, oxy-species) were used in the indium-mediated coupling reaction with aldehydes giving **1.67** with moderate to good yields in water.[51] (Scheme 1.28)



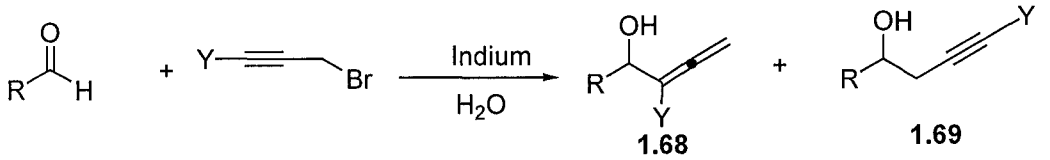
Scheme 1.27



Scheme 1.28

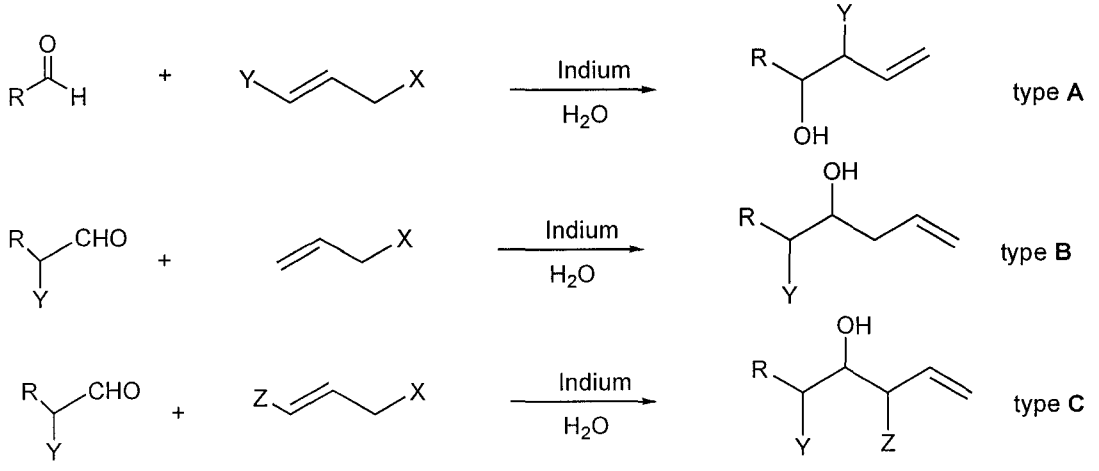
The reaction has also been expanded to propargylation and allenylation of aldehydes. Unlike the tin-mediated reaction, the indium-mediated coupling of aldehydes with propargyl bromides occurred regioselectively in aqueous media to give preference

of either homopropargyl or allenylic alcohols depending on the γ-substituent of the propargyl bromide.[52]



Scheme 1.29

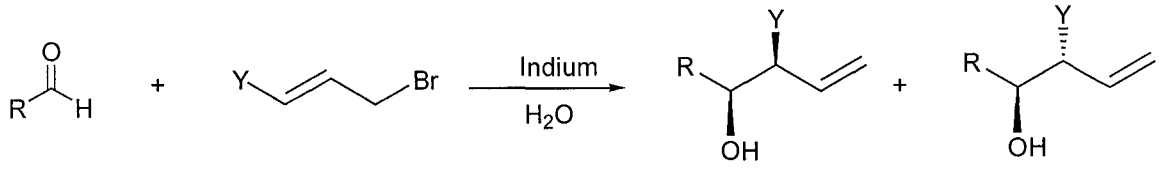
1.3.3.2 Diastereoselectivity: With respect to the diastereoselectivity, generally, three types of situations, **A**, **B** and **C** are possible. (Scheme 1.30)

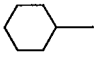


Scheme 1.30

In the type **A** situation, the diastereoselectivity depends on the substituents of the aldehyde and the allylic halide, but not on the geometry of the double bond of the allylic halide. For example, in the case of using E or Z-cinnamyl bromide, similar distereoselectivities were obtained regardless of the geometry of the double bond.[53] It

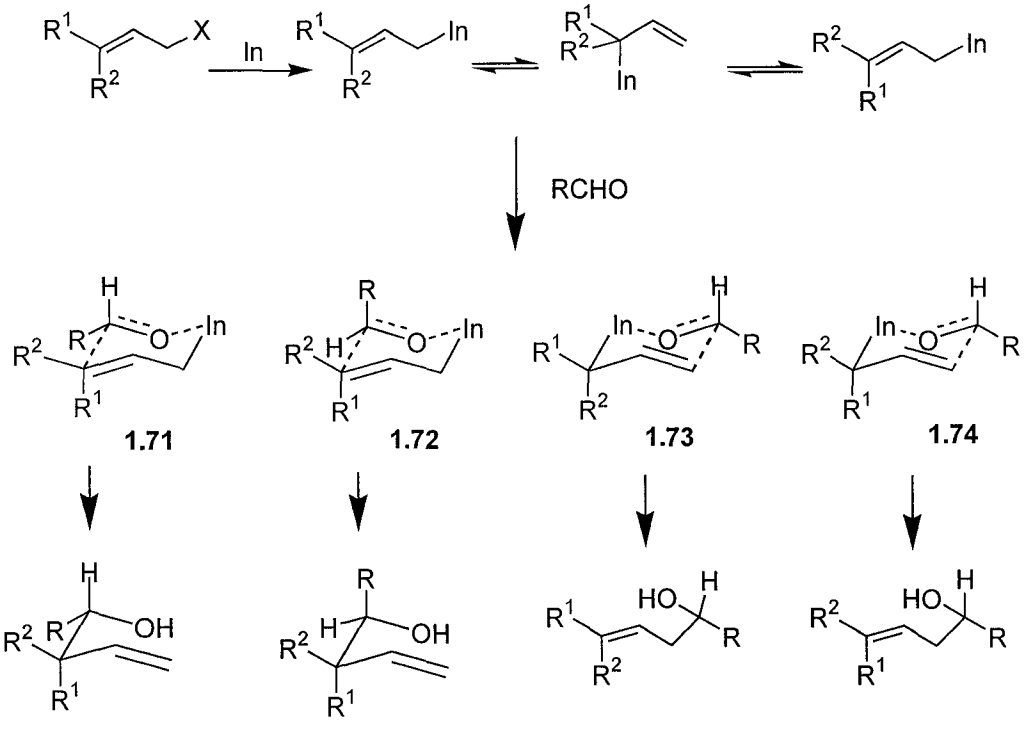
was found that the *anti*-diastereoselectivity increased with the increasing size of substituents. (Scheme 1.31)



	R	syn	*anti*
Y=Me	Ph	50	50
$Y=CO_2Me$	Ph	16	84
Y=Ph	Ph	4	96
	$n\text{-}C_6H_{13}$	31	69
	i-Pr	4	96
		10	90

Scheme 1.31

The selectivity in type **A** can be accounted for by Zimmerman type transition states involving the allylindium species and the carbonyl compounds. (Scheme 1.32) Apparently, when the substituent (R_1 or R_2) is bulky, the cyclic transition state **1.73** or **1.74** is preferred. Otherwise, for most substituents, transition state **1.71** or **1.72** predominates. Thus, the diastereoselectivity is governed by the steric size of the substituent on aldehyde (R). In general, the *anti* product would be favored.



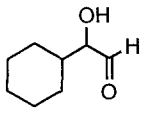
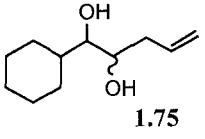
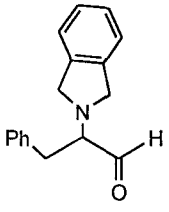
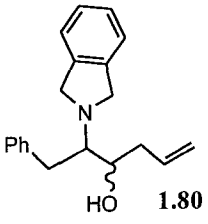
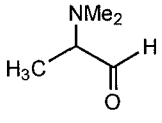
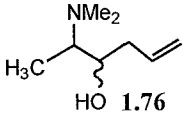
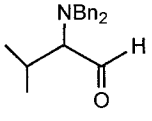
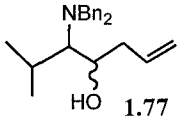
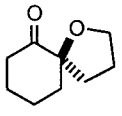
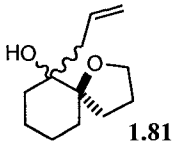
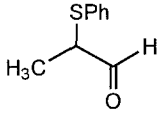
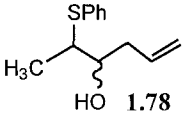
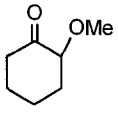
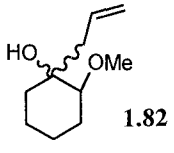
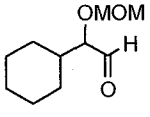
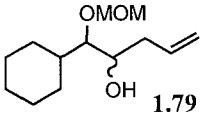
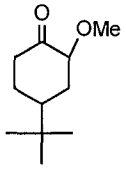
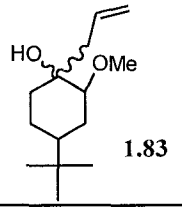
Scheme 1.32

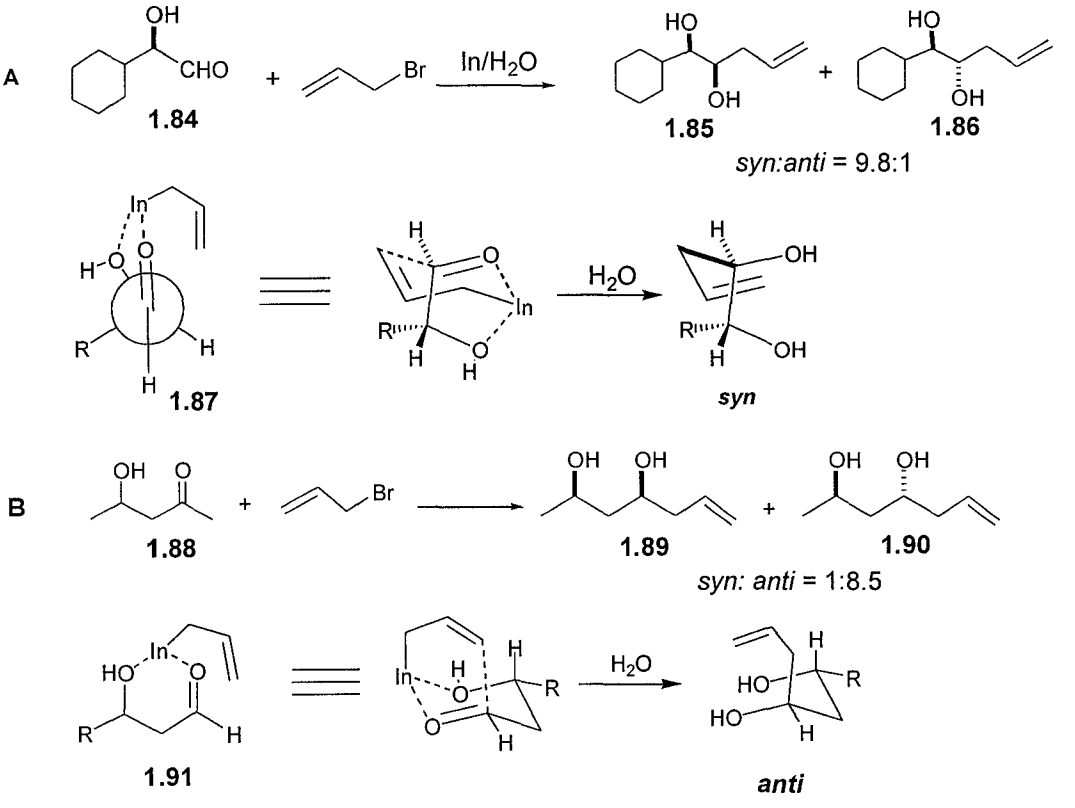
In the type **B** situation, either *syn* or *anti* diastereoselectivity can be favored depending on the properties of the α-substituents Y. In the presence of a strong chelating group, such as a hydroxyl group, the reaction generally leads to a preference of *syn* product (Table 1.1, **1.75**, **1.76**, **1.82**, **1.83**), whereas in the case of Y as a non-chelating group, the reaction gives mainly *anti* product (Table 1.1, **1.77**, **1.78**). However, the presence of an α-alkoxyl group (a weak chelating group) often leads to a higher ratio of non-chelating product (**1.79**, **1.81**) in the reaction. These observations, which has been investigated extensively by Paquette's group, provide an efficient strategy for the diastereofacial control of indium-mediated allylation in aqueous media.[54]

To account for the stereochemical results, it has been suggested that in the case of α-hydroxyl substituted aldehydes, the allylindium intermediate coordinates with both the carbonyl function and the hydroxyl function as in **1.87** leading to the *syn* adduct.

(Scheme 1.33A) Similarly, *anti*-selectivity can also be accounted for in the case of β-hydroxyl substituted aldehydes. (Scheme 1.33B)

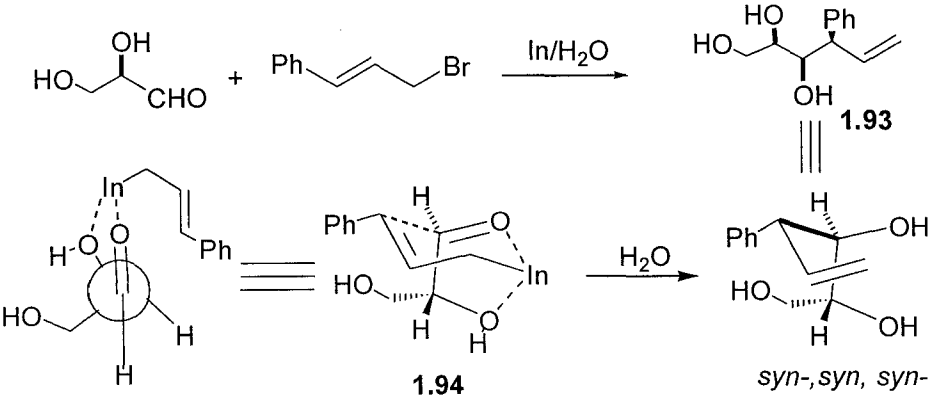
Table 1.1 Selected Examples of Indium-mediated Chelation/non-chelation Allylation of Aldehyde with Allyl Bromide in Water

Substrate	Allylation products	chelate:non-chelate	Substrate	Allylation products	chelate:non-chelate
	 **1.75**	9.8:1		 **1.80**	8.2:1
	 **1.76**	99:1			
	 **1.77**	1:4		 **1.81**	2.7:1
	 **1.78**	1:4		 **1.82**	12.5:1
	 **1.79**	2.1:1		 **1.83**	>97:3



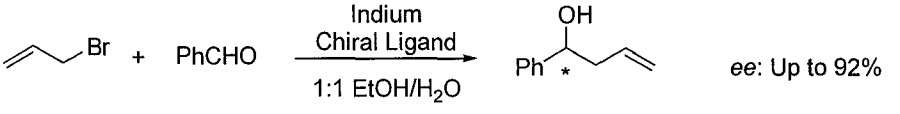
Scheme 1.33

In type **C**, the situation is much more complicated and multi-stereogenic centers are formed. One example for this type is the reaction of unprotected glyceraldehyde with cinnamyl bromide. The *syn syn syn-* isomer is formed preferentially in this case. A cyclic transition state **1.94** was proposed which involves the chelation of the allylindium species with the α-hydroxyl of glyceraldehydes.[55] (Scheme 1.34)

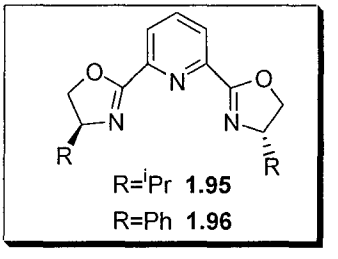


Scheme 1.34

1.3.3.3 Asymmetric Induction: Despite the extensive studies of diastereocontrol of indium-mediated Barbier-type allylation reaction in aqueous media, there had been few reports for the enantioselective control for the C-C formation of this reaction. Recently, encouraging results were reported by Loh's group. (Scheme 1.35) By using (S, S)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine (**1.95**) as the chiral ligand, an enantioselective allylation of aldehydes with *ee* up to 92% can be realized with aqueous indium-mediated Barbier-type reactions. In this case, the involvement of Lewis acid such as cerium(IV) triflate is found to be helpful for the improvement of the yields and enantioselectivity.[56] To our knowledge, this is the first and the only report for the enantioselective indium-mediated allylation reaction in aqueous media.

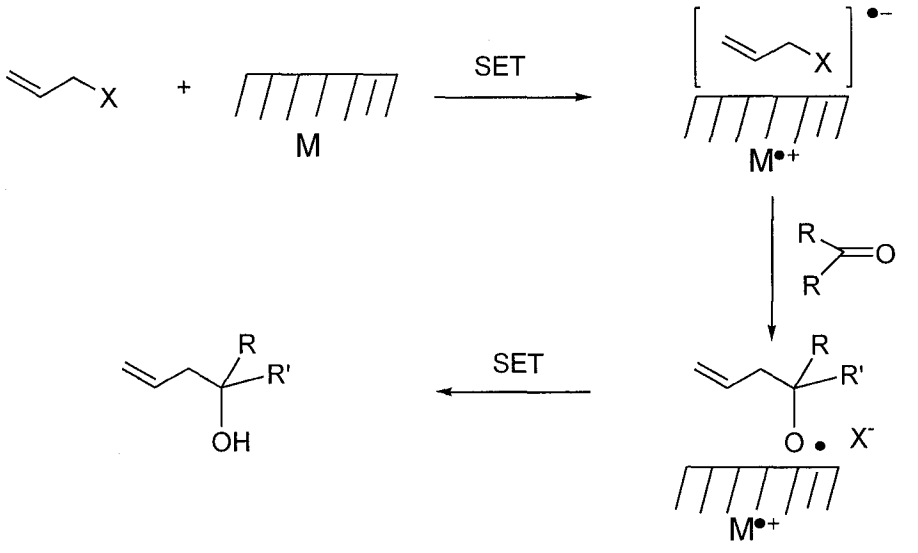


Chiral Ligand:



Scheme 1.35

1.3.3.4 Mechanistic Investigations. When the reaction was first discovered, a single electron transfer (SET) mechanism had been proposed. It was suggested that a reactive radical anion species was generated on the surface of the metal, and was responsible for the reaction.[57] (Scheme 1.36)



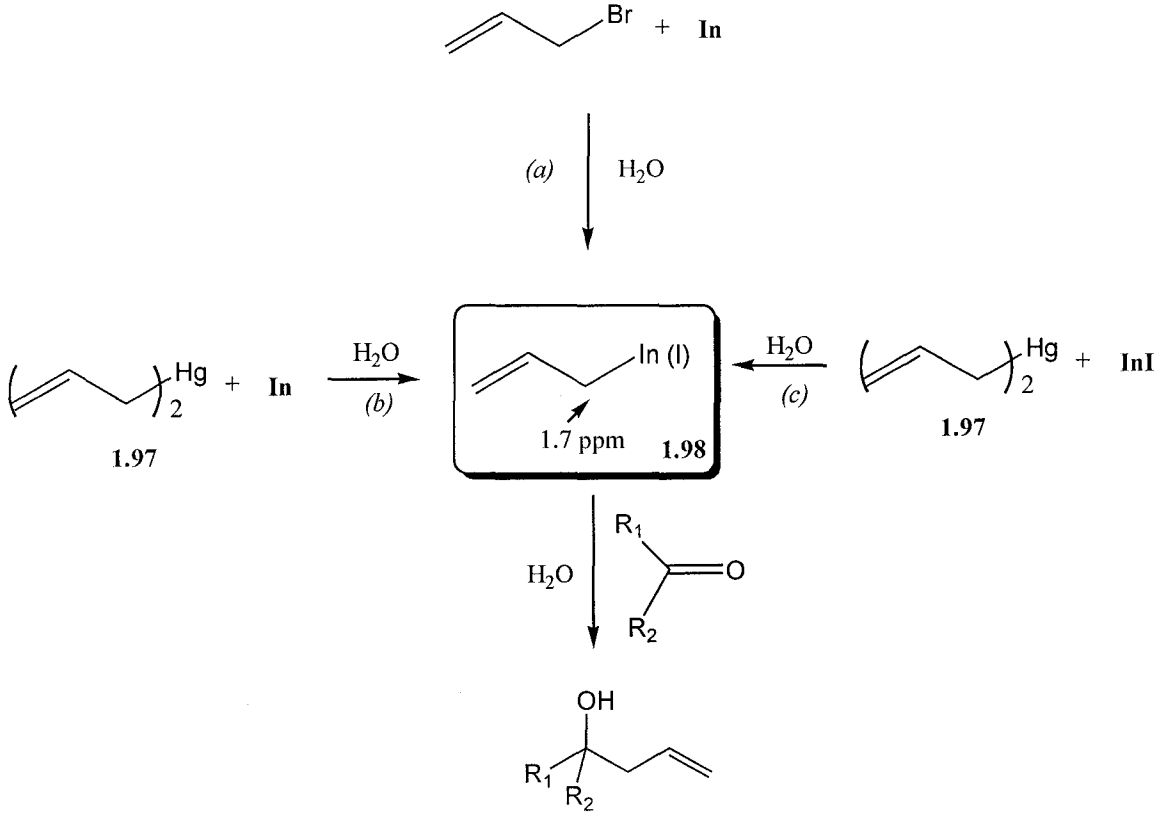
Scheme 1.36

Subsequently, the existence of an allylindium intermediate is considered likely through the observation of Whitesides *et al.*[58] The presumed allylindium dichloride, which generated from the reaction of allylmagnesium bromide and indium trichloride in ether, could react with carbohydrates in ethanol/water (10/1) to give the corresponding homoallylic alcohols.

Recently, the nature of the organoindium intermediate was elucidated by Chan and Yang as allylindium (I). (Scheme 1.37) They found that by stirring indium powder and allyl bromide together in D_2O, an indium species was generated and it showed a characteristic proton doublet at 1.7ppm. The same intermediate could be generated through another two pathways: by the aqueous transmetalation reaction of diallylmercury with indium or indium (I) iodide.[59] They argued that a transient but discrete allylindium (I) was formed.

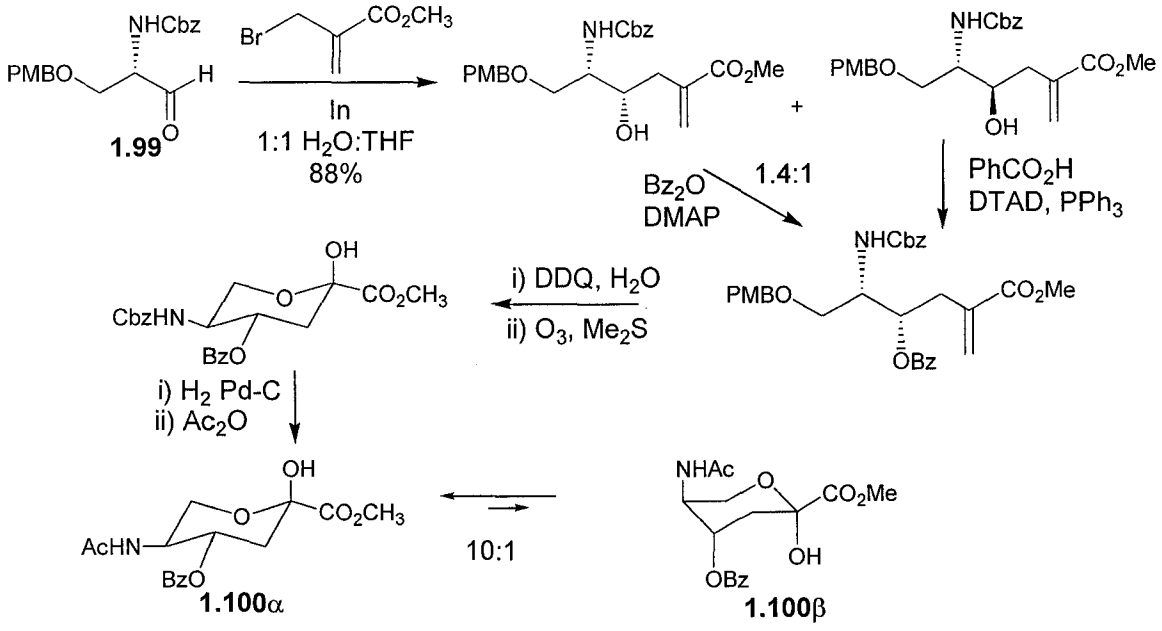
Although this conclusion did not rule out the possibility of a parallel process involving the metal surface allyl radical anion, the formation of an indium(I) instead of

an indium(III) species is consistent with the fact that indium has a relatively low first ionization potential.



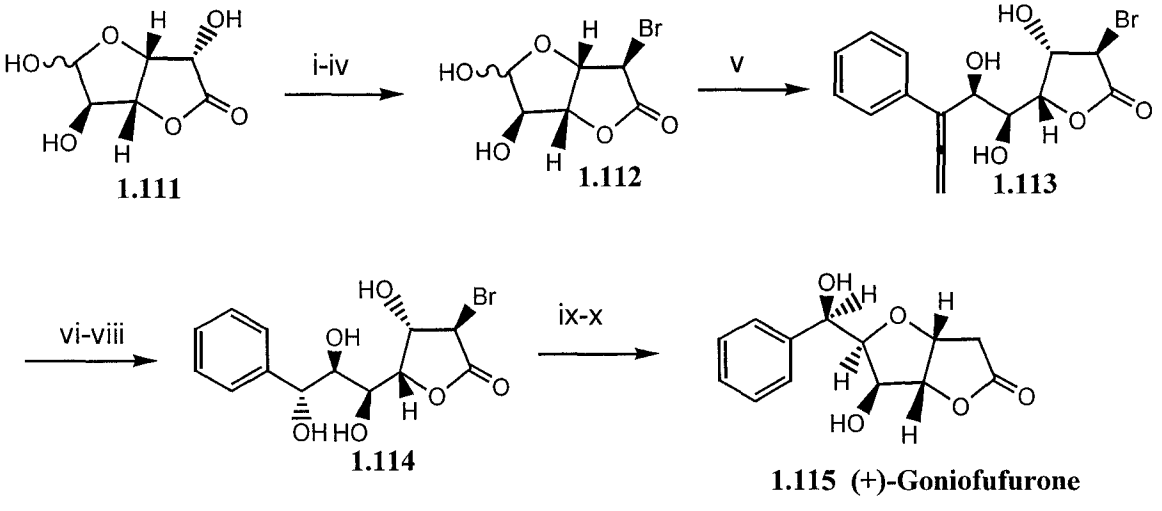
Scheme 1.37

1.3.3.5 Synthetic Applications. The most common application of this reaction in organic synthesis is in carbohydrate synthesis. As an outgrowth of this chemistry, there is a development of aqueous strategy towards the synthesis of sialic acids and its analogues. Besides the syntheses of KDN and N-acetylneuraminic acid,[60] the phosphoric acid analogues[61] have also been synthesized using the indium-mediated coupling of the lower carbohydrates with dimethyl 3-bromopropenyl-2-phosphonate in water. A recent example is the synthesis of the six-carbon sialic acid **1.110** reported by Halcomb *et al.*[62] (Scheme 1.38)



Scheme 1.38

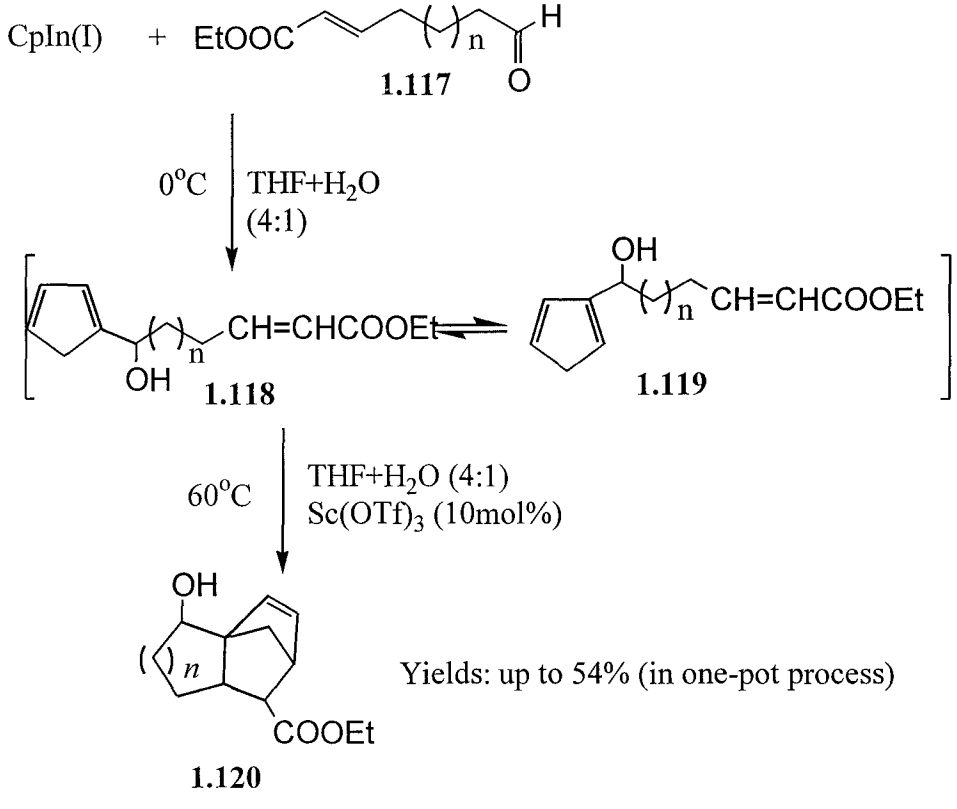
The aqueous indium-mediated allenylation reaction has also been employed in the synthesis of (+)-Goniofufurone reported by Li *et al.*[63] (Scheme 1.39)



i) acetone, H_2SO_4, rt 86%; ii). Tf_2O, Py, CH_2Cl_2, 40 °C, iii)LiBr, acetone; iv) TFA-H_2O; v) phenyl propargyl bromide, In, 0.1N HCl/EtOH (1:9); vi) O_3, MeOH, then Me_2S; vii) $NaBH_4$, MeOH; viii) H_2SO_4, Ac_2O, for 3 steps; ix) Na_2SO_3, MeOH-H_2O; x) HCl(g), MeOH

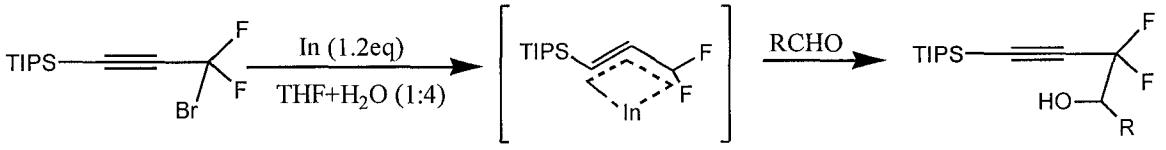
Scheme 1.39

The existence of the allylindium(I) intermediate in indium-mediated aqueous organometallic reaction established by Chan and Yang also led them to the examination of other organoindium(I) compounds with electrophiles in aqueous media. Cyclopentadienylindium(I) was found to be a nucleophilic reagent, which can react with aldehydes or electron-deficient alkenes in aqueous media to give functionalized substituted cyclopentadienes. This reaction with the appropriate substrates can be followed by an intramolecular Diels-Alder reaction in the same pot to provide complex tricyclic structures **1.120** in a synthetically efficient manner.[64] (Scheme 1.40)



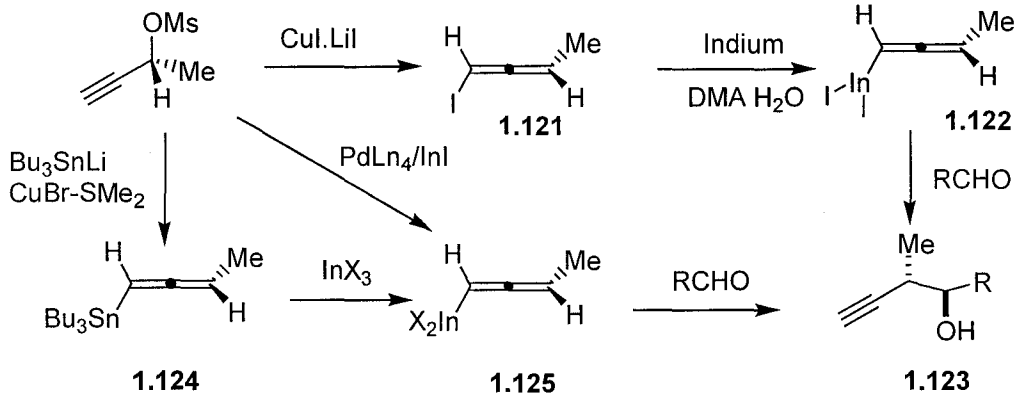
Scheme 1.40

More recently, Hammond[65] *et al.* reported that a stable difluoroallenyl indium species could be generated in aqueous media and this species could further react with aldehydes to give homopropargylic gem-difluoro alcohols in good yields. (Scheme 1.41)



Scheme 1.41

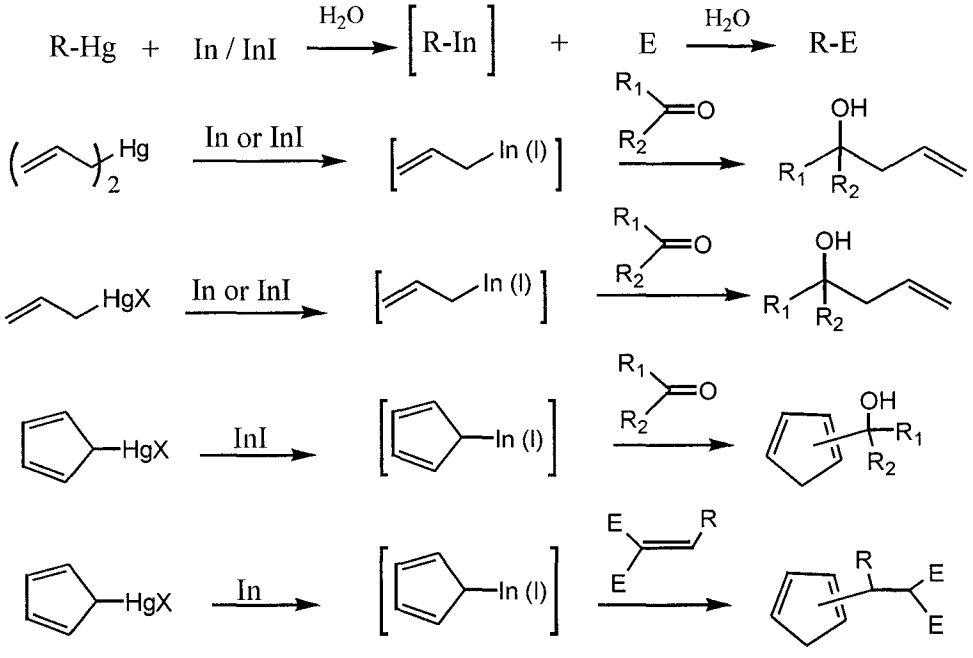
1.3.3.6 Transmetalation reactions. Besides the direct reaction of indium with organic halides, it has been known that organoindium compounds can be generated through transmetalation with other organometallics. Recently, aqueous transmetalation has been used to generate organoindium compounds. Marshall[66] *et al.* reported that the allenyl iodide **1.121** reacted with indium in DMA/H_2O to give the presumed allenylindium intermediate, which coupled with aldehydes to give the corresponding homopropargyl alcohols **1.123**. (Scheme 1.42) Similar allenylindium species appeared to have been generated from the allenyltin **1.124** with InX_3.



Scheme 1.42

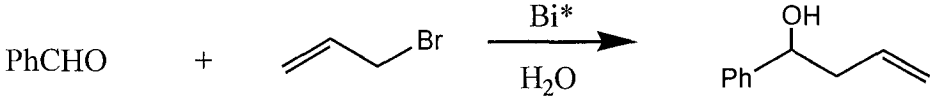
Yang and Chan found that organoindium(I) can be generated *in situ* from the aqueous transmetalation reaction of organomercury and indium. And the organoindium reagent thus generated can undergo nucleophilic addition to carbonyl compounds or

electron deficient alkenes. Interestingly, such transmetalation can be dramatically accelerated by using water alone as reaction media.[67] (Scheme 1.43)



Scheme 1.43

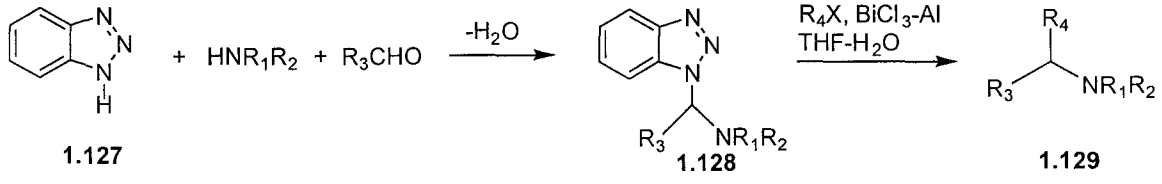
1.3.4 Bismuth-Mediated Aqueous Organometallic Reactions



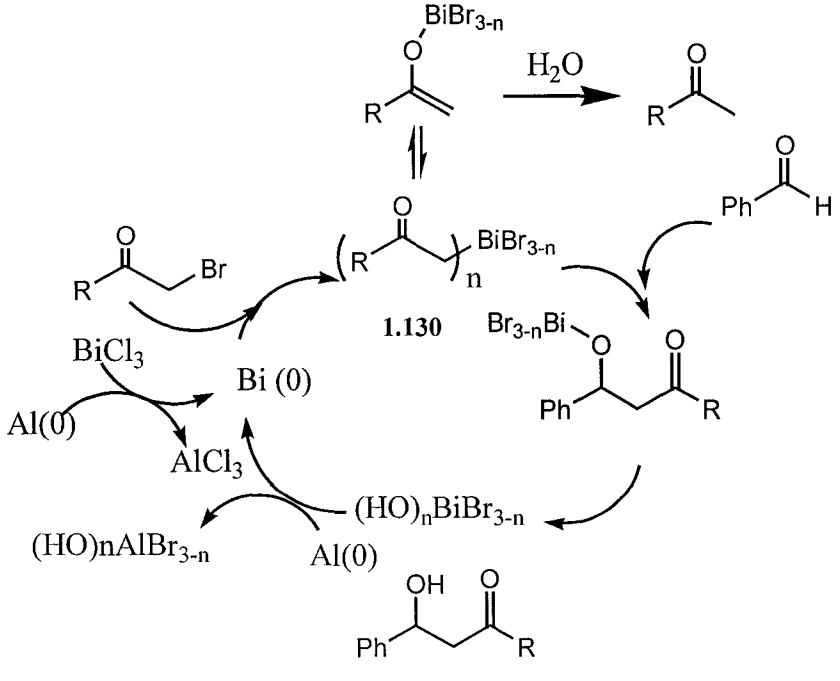
Bi* can be generated in situ by following combination:
Al (0)/$BiCl_3$, Zn(0)/$BiCl_3$, Fe(0)/$BiCl_3$, Sm(0)/BiCl3, $NaBH_4$/$BiCl_3$

It has been recently found that bismuth can also mediate the Barbier-Grignard-type reaction in aqueous media. Wada[68] reported that metallic bismuth could be used for the aqueous Barbier type allylation similar to the method used for tin, in which aluminum powder or hydrobromic acid was used as the promoter. Later, it was found that the activated bismuth metal could be generated by using of a combination of active metal and

bismuth (III). Such combination includes Al(0)/$BiCl_3$, Zn(0)/$BiCl_3$, and Fe(0)/$BiCl_3$ etc. Katritzky[69] reported that the Bi(III)/Al could mediate the allylation or alkylation of immonium cation to give amines (Scheme 1.44). Shen[70] *et al.* found that the Bi(III)/Al system can mediate the Reformatsky type reaction in aqueous media. In the reaction, only catalytic amount of $BiCl_3$ is needed. It was presumed that acylbismuth reagent **1.130** is formed through the oxidative addition of α-bromoketone to Bi (0) generated by the reduction of $BiCl_3$ with Al (0). (Scheme 1.45) A more recent example was reported by Zhang.[71] By using Bi(III)/Sm, benzyl sulfides and selenides were synthesized via reaction of benzyl bromide with disulfides and diselenides in aqueous media.



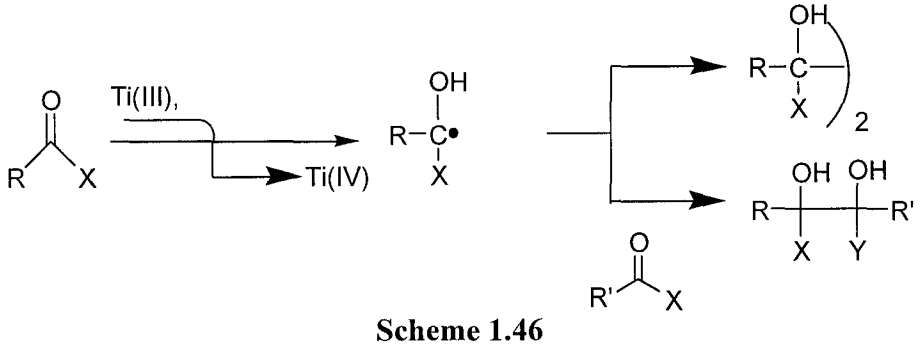
Scheme 1.44



Scheme 1.45

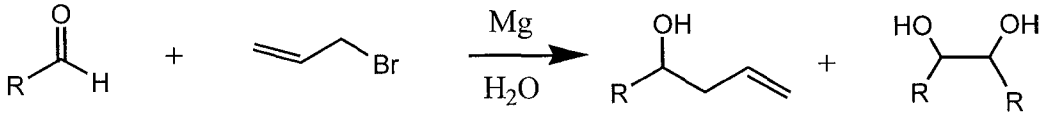
1.3.5 Reactions With Other Metals

Lead[72] and cadmium[73] can also mediate the Barbier type allylation. These metals are much less reactive than the metals discussed previously. Clerici and Porta[74] extensively studied the aqueous pinacol coupling reactions mediated by Ti(III) via a radical process. Aromatic ketones or aldehydes were homo- or cross-coupled by $TiCl_3$ in aqueous media under basic conditions. (Scheme 1.46)



Scheme 1.46

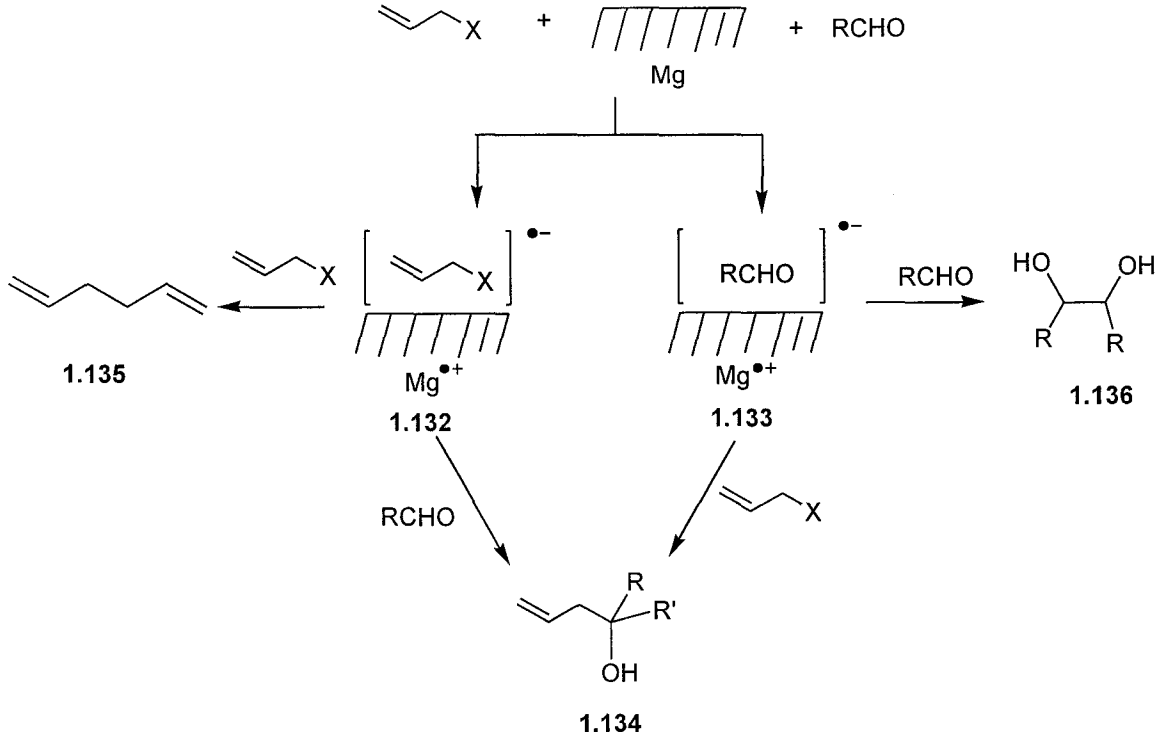
Li[75] *et al.* reported the pinacol coupling of aryl aldehydes in the presence of manganese in water. The combination of manganese and copper was found to be highly effective mediator for the allylation of aryl aldehydes in water. The combination manganese/cupric chloride can also mediate the homo- or cross-coupling of alkyl halides in aqueous media to give the dimerization products in good yield.[76]



Scheme 1.47

In view of the high reactivity of organomagnesium reagents toward water, it was thought that magnesium could not be used for such a reaction. An unexpected Barbier-Grignard allylation of aldehydes with magnesium in water was reported by Li[77] *et al.* (Scheme 1.47) The contact of water and the metal surface would prohibit the formation

of the organomagnesium reagent. An SET mechanism was tentatively proposed. The transfer of electrons from magnesium to the allyl halide or aldehyde generates the corresponding radical anions **1.132** and **1.133**. Further reaction of these generated radical species with either substrate can leading to the allylation product **1.134**, Wurtz coupling product **1.135**, and pinacol coupling product **1.136**. (Scheme 1.48)



Scheme 1.48

1.4 Research Proposal

In spite of extensive exploration since the first discovery, the full potential of the metal-mediated aqueous organometallic reactions is still far from being fully realized. From the methodology point of view, the development of this chemistry needs to extend to other electrophiles such as C=N electrophiles. The factors that affect the

stereochemistry of the reaction need to be better understood. Halides with diverse structures for the generation of the organometallic intermediates may yet to be explored. Moreover, with the growth of this chemistry, more applications and its advantages should be demonstrated in organic synthesis.

In the following chapters, we will demonstrate the expansion of this chemistry to activated C=N electrophiles and the exploration of its stereochemical control. We will also demonstrate our effort in searching for variations of the reaction. The application in organic synthesis will also be presented in the following chapters.

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Chapter 2

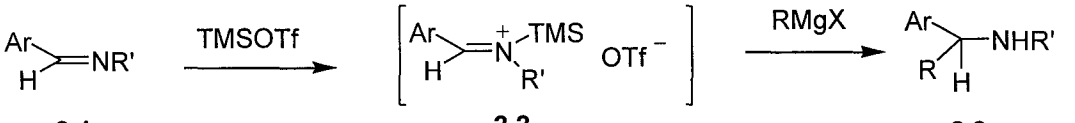
Metal-mediated Aqueous Barbier-type Allylation of Activated C=N Electrophiles

2.1 Introduction

2.1.1 Nucleophilic Addition of Imines and Imine Derivatives. An Overview

The nucleophilic 1,2-addition of organometallic regents to C=N double bonds is a valuable method for the synthesis of primary and secondary amines. However, compared to the carbonyl compounds, the development of these additions were restricted both by the poor electrophilicity of the azomethine carbon and by the tendency of enolizable imines and imine derivatives to undergo deprotonation rather than addition. Although a systematic evaluation of the relationship between azomethine structure and reactivity with carbanions has not been reported, it is implicit that the electrophilicity of imines can be increased by N-alkylation to form highly reactive iminium salts, by N-oxidation to form reactive nitrones, or by N-acylation or N-sulfonylation to form reactive acylimines and sulfonimines.

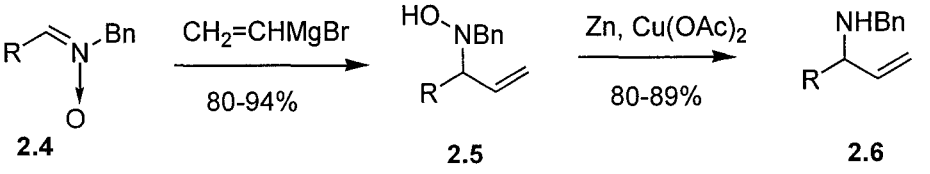
Brook[1] *et al* reported that the use of trimethyl silyl triflate (TMSOTf) could improve the yield of the addition of organomagnesium reagents to several arylaldimines. The mechanism proposed involves the formation of an iminium salt **2.2**. (Scheme 2.1)



2.1 **2.2** **2.3**

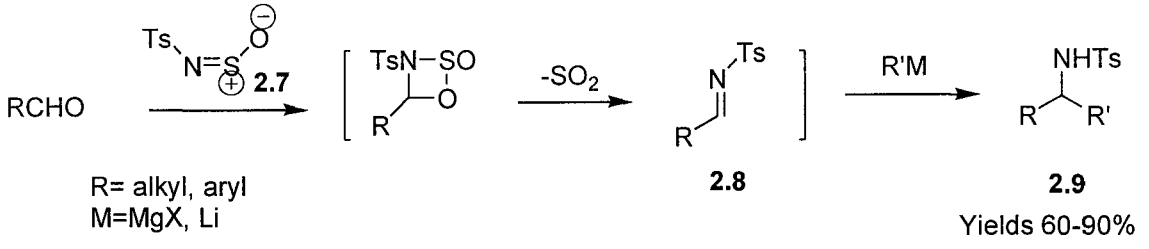
Scheme 2.1

Dondoni[2] *et al* reported an efficient synthesis of secondary allylamines via addition of vinylmagnesium bromide to a variety of alkyl or aryl nitrones. (Scheme 2.2)



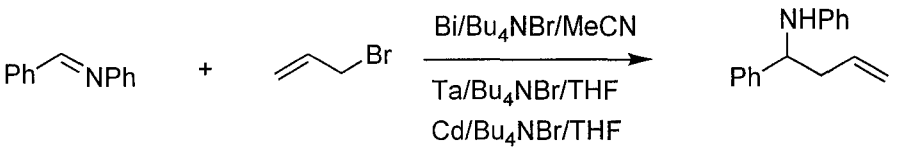
Scheme 2.2

The addition of the Grignard and organolithium reagents to N-sulfonyl aldimines **2.8** generated *in situ* from aldehydes and N-sulfinyl sulfonamides **2.7** proved to be quite efficient to give sulfonamide **2.9**.[3] (Scheme 2.3)



Scheme 2.3

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 transformation of the C=C bond of the allyl moiety. The Barbier procedure for imine allylation involving the formation of the allylmetal reagent *in situ*, has been the subject of significant advances in recent years. For example, cadmium, bismuth and tantalum[4] mediated allylations of aldimines take place with good (Ta) to excellent (Cd, Bi) yields, under very mild conditions. (Scheme 2.4)



Scheme 2.4

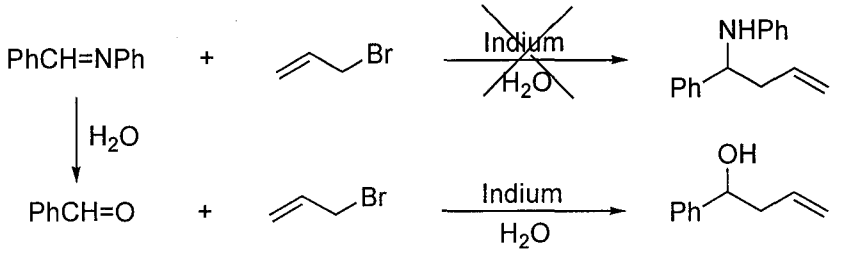
Despite the extensive exploration of nucleophilic addition of imines and imine derivatives, the reactions are all conducted in organic solvent systems. From the green chemistry point of view, water as an alterative reaction medium, offers many advantages for conducting reactions over traditional organic solvent. We have therefore examined the feasibility of performing this chemistry in aqueous media.

2.1.2 The Difficulties Associated with C=N Electrophiles in Aqueous Media

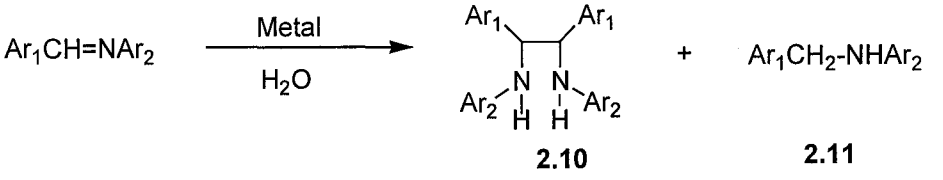
The discovery of the new indium chemistry has led to an impressive progress in aqueous organometallic reactions especially in aqueous allylation reaction with carbonyl compounds. It may have been noticed that the success of this reaction was still limited to C=O electrophiles. In spite of the fact that allylation of C=N electrophiles can lead to the formation of homoallylic amines as potential building blocks in organic synthesis,[5] the development of such addition of organometallic reagents to C=N bonds in aqueous media was severely limited.[6] The difficulties for such addition are basically associated with the following properties of C=N electrophiles in comparison with that of C=O electrophiles. First of all, azomethine carbon is generally less electrophilic than the corresponding carbonyl compound, and as a result, is less reactive towards nucleophilic reagents. Secondly, aldimines can be hydrolyzed under aqueous reaction condition giving the corresponding carbonyl compounds.[7] Thus, preliminary attempts of the Barbier-type

allylation reaction of aldimines in aqueous media with indium led to the formation of homoallylic alcohols instead of the expected amines in water.[8] Thirdly, aldimines are also known to readily undergo the coupling and reduction reaction in aqueous media in the presence of metals. For example, aqueous metal-mediated coupling reaction of imines has been reported giving the corresponding 1,2-diamines **2.10**.[9] (Scheme 2.5)

Problem 1: The Hydrolysis of C=N Bond



Problem 2: Coupling and Reduction



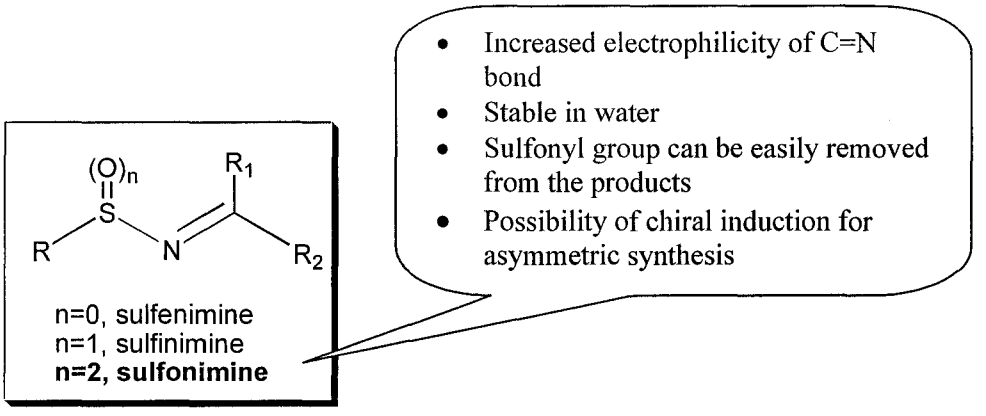
2.10 **2.11**

Scheme 2.5

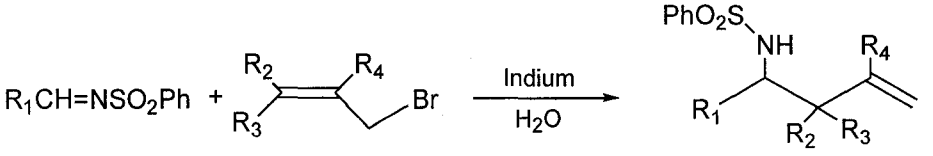
2.1.3 The Role of Sulfonimines in Organic Synthesis

To circumvent these problems, our strategy is based on the consideration that the electrophilicity of the azomethine carbon atom of the C=N function can be increased by introducing electron-withdrawing groups via N-oxidation, N-acylation or N-sulfonylation.[10] Therefore, if the rate of the allylation reaction of C=N electrophiles is increased to be faster than the rate of hydrolysis of C=N eletrophile, then the desired homoallylic amine may be obtained.

In general, sulfonimines are more electrophilic and more stable to hydrolysis in comparison with the aldimines. Furthermore, the sulfonyl group can be readily removed from the allylation products to give the corresponding primary amines, which gives more room for application of this method in organic synthesis.[11] Finally, sulfonimines may be chirally modified and chiral sulfonimines have been employed in asymmetry synthesis.[12]



Based on these considerations, the first step of our investigation is focused on the indium-mediated allylation of sulfonimines. (Scheme 2.6)



2.12 **2.13** **2.14**

Scheme 2.6

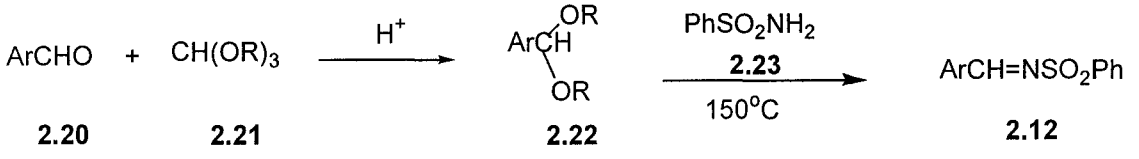
2.2 Allylation of Sulfonimines Mediated by Indium

2.2.1 Preparation of Sulfonimines

Three methods had been reported for the preparation of sulfonimines. The first method reported by Davis[13] *et al* was the reaction of neat aromatic aldehyde acetal with

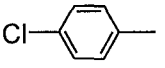
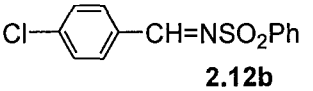
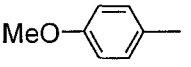
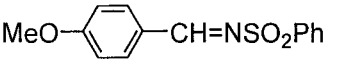
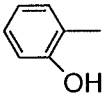
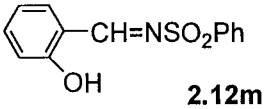
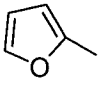
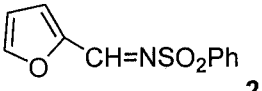
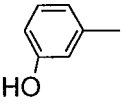
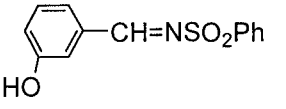
benzene sulfonamide at 150 °C. (Scheme 2.7). A better yield was obtained when benzaldehyde ethyl acetal was used instead of the methyl acetal. (Table 2.1, *entries 1 and* 2) Electron-withdrawing group seemed to increase the reactivity of the substrate, and hence, a higher yield of sulfonimine was obtained (*entries 1 and 3*). However, in the case of 2-furaldehyde ethyl acetal, the reaction gave mainly decomposition products due to the high temperature and the sensitivity of the furan ring to oxidation. (*entry* 6). As 3-hydroxybenzaldehyde dimethyl acetal is a solid, the reaction was difficult to perform since the reaction needed to proceed in a neat form. *(entry 7*).

Boger[14] *et al* reported that various aryl or aliphatic sulfonimines could be prepared by the reaction of the aldehydes with benzenesulfonamide promoted by titanium tetrachloride in the presence of triethylamine as base. (Scheme 2.8) The reaction worked equally well for both aromatic (Table 2.2, *entries 1~3*) and aliphatic aldehydes (*entries 4~5*).



Scheme 2.7

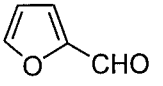
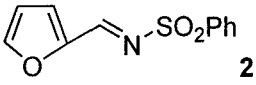
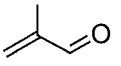
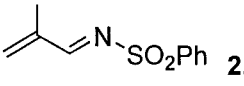
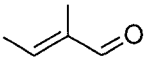
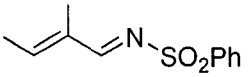
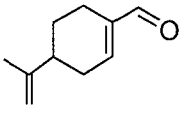
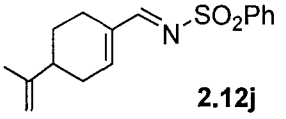
Table 2.1 Synthesis of Sulfonimines by Method A

Entry	Ar	R	sulfonimine	Yield%
1	Ph	Me	$PhCH=NSO_2Ph$ **2.12a**	30
2	Ph	Et		95
3		Me	 **2.12b**	99
4		Et	 **2.12c**	90
5		Me	 **2.12m**	50
6		Et	 **2.12d**	20
7		Me		trace, SM recovered

As the Boger's method can only offer the α,β-unsaturated aliphatic sulfonimines, the method developed by Trost[15] *et al* was adopted to obtain the saturated aliphatic sulfonimines. (Scheme 2.9) Two aliphatic tosylimines **2.12f** and **2.12i** were obtained with high yields. Furthermore, it is worth noting that the preparation of aliphatic tosylimines was restricted to those from non-enolizable aldehydes since tosylimines bearing α-proton undergo facile isomerization to give the corresponding unsaturated sulfonamides. (Scheme 2.10)

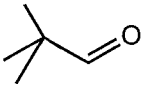
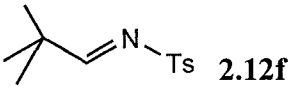
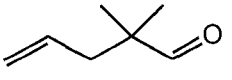
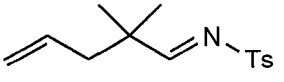
$$RCHO + PhSO_2NH_2 \xrightarrow[CH_2Cl_2,\ 0\ ^\circ C]{TiCl_4,\ Et_3N} RCH{=}NSO_2Ph$$

Table 2.2 Preparation of Sulfonimines by Method B

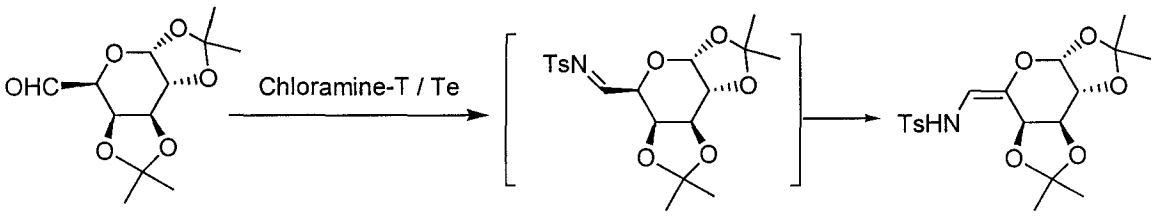
entry	aldehyde	Product	yield (%)
1	PhCHO	$PhCH{=}NSO_2Ph$ **2.12a**	85
2		 **2.12d**	80
3	PhCH=CHCHO	$PhCH{=}CH{-}CH{=}NSO_2Ph$ **2.12e**	82
4		 **2.12g**	85
5		 **2.12h**	83
6		 **2.12j**	89

Scheme 2.8

$$2\ RCHO + 2\ TsN(Cl)Na + Te \longrightarrow 2\ RCH{=}NTs + 2\ NaCl + TeO_2$$

aldehyde	product	yield (%)
	 **2.12f**	85
	 **2.12i**	92

Scheme 2.9



2.25 **2.26** **2.27**

Scheme 2.10

With all these sulfonimines in hand, we can now proceed to study the allylation reaction of these substrates.

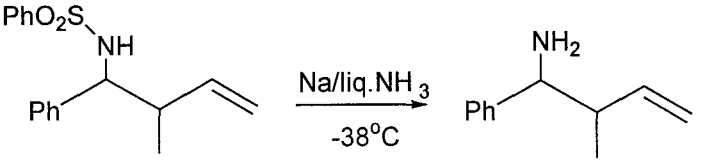
2.2.2 Reactivity

The indium-mediated Barbier-type allylation reaction of sulfonimines (**1**) was first examined.[16] (Table 2.3)

Mediated by indium, allylation reaction of sulfonimines can be performed smoothly with allyl bromide. Homoallylic sulfonamides (**2.14**) were obtained in high yields (*entries* 1-15). The allylation can be carried out either in organic solvents, in pure water (*entries* 1-4) or in aqueous organic solvent mixtures. In those cases where the solid sulfonimines had low solubility in water, adding some THF to the aqueous media was helpful for an increased yield. The optimal media for this allylation reaction seemed to be 1:1 mixture of THF and water. For aromatic sulfonimines, the substituted group on the benzene ring, either electron withdrawing or electron donating, appeared to have little influence on the reaction. Indium-mediated aqueous Barbier-type allylation of aliphatic sulfonimines was also examined (*entries* 11-15). Although the expected products were obtained, the aliphatic sulfonimines were less reactive than the aromatic sulfonimines in

this reaction, and the reaction needed longer reaction time, with relatively lower yields obtained.

By using sodium in liquid ammonia, the sulfonyl group on the allylation product can be smoothly cleaved and primary homoallylic amine was obtained cleanly with high yield.[17] We demonstrated this with the conversion of **2.14d** to **2.15** in 90% of yield. (Scheme 2.11)

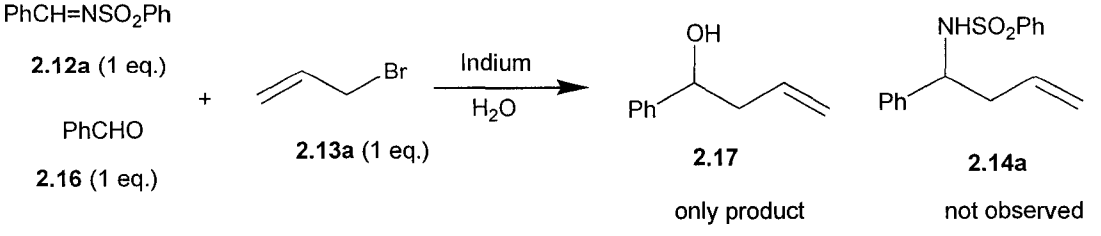


2.14d **2.15**: 90% yield

Scheme 2.11

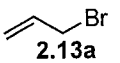
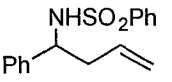
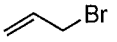
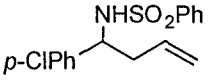
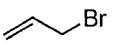
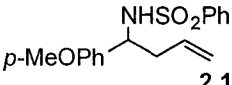
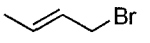
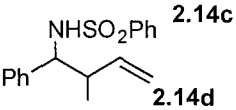
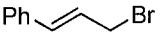
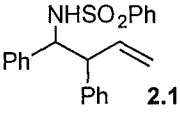
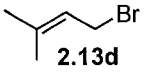
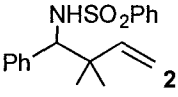
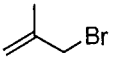
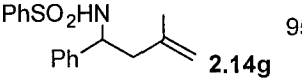
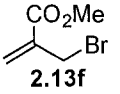
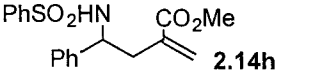
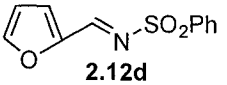
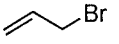
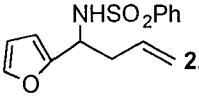
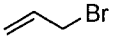
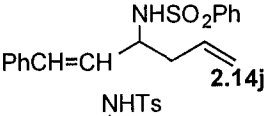
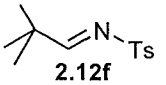
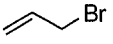
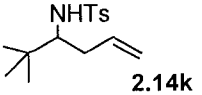
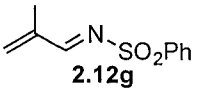
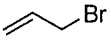
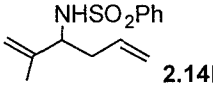
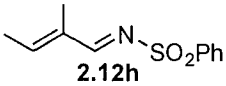
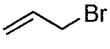
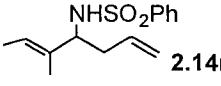
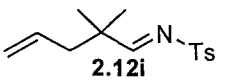
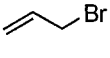
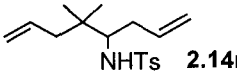
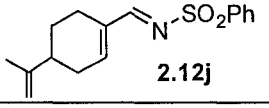
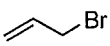
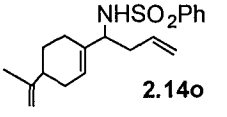
2.2.3 Chemo-selectivity

We have compared the reactivity of sulfonimines with that of the corresponding carbonyl compounds. When a one to one ratio of sulfonimine **2.12a** and benzaldehyde (**2.16**) was reacted with 1 equivalent of allylbromide and indium (1 eq.), only the homoallylic alcohol **2.17** was obtained without any observation of homoallylic sulfonamide **2.14a**. The sulfonimine **2.12a** and unreacted benzaldehyde **2.16** were recovered. (Scheme 2.12) This result suggests that sulfonimine is far less reactive than the corresponding aldehyde.



Scheme 2.12

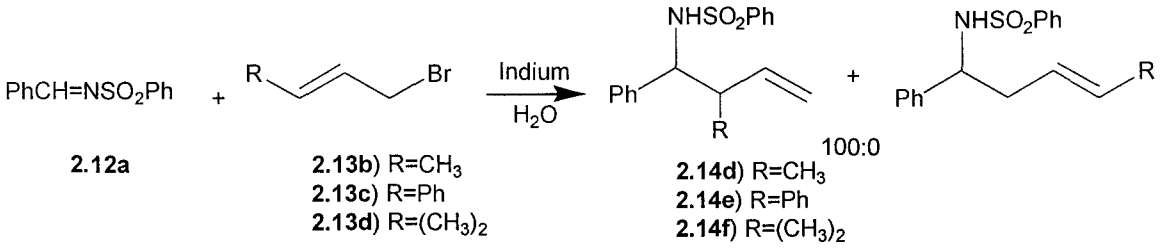
Table 2.3 Indium-mediated Allylation Reaction with Sulfonimines

Entry	Sulfonimine	Allyl Bromide	Solvent	Product	Yield%[a]
1	PhCH=NSO$_2$Ph **2.12a**	 **2.13a**	THF Dioxane DMF H$_2$O	 **2.14a**	99[b] 99[b] 99[b] 95
2	*p*-ClPhCH=NSO$_2$Ph **2.12b**		H$_2$O H$_2$O:THF= 3:1	 **2.14b**	50[b] 95
3	*p*-MeOPhCH=NSO$_2$Ph **2.12c**		H$_2$O H$_2$O:THF= 3:1	 **2.14c**	80[b] 95
4	PhCH=NSO$_2$Ph	 **2.13b**	H$_2$O	 **2.14d**	92[c]
5	PhCH=NSO$_2$Ph	 **2.13c**	H$_2$O:THF= 1:1	 **2.14e**	85[d]
6	PhCH=NSO$_2$Ph	 **2.13d**	H$_2$O:THF= 1:1	 **2.14f**	55
7	PhCH=NSO$_2$Ph	 **2.13e**	H$_2$O:THF= 1:1	 **2.14g**	95
8	PhCH=NSO$_2$Ph	 **2.13f**	H$_2$O:THF= 1:1	 **2.14h**	30
9	 **2.12d**		H$_2$O:THF= 1:1	 **2.14i**	97
10	PhCH=CH-CH=NSO$_2$Ph **2.12e**		H$_2$O:THF= 1:1	 **2.14j**	90
11	 **2.12f**		H$_2$O H$_2$O:THF= 1:1	 **2.14k**	<5 50
12	 **2.12g**		H$_2$O H$_2$O:THF= 1:1	 **2.14l**	35[b] 90
13	 **2.12h**		H$_2$O H$_2$O:THF= 1:1	 **2.14m**	40[b] 85
14	 **2.12i**		H$_2$O H$_2$O:THF= 1:1	 **2.14n**	<5 60
15	 **2.12j**		H$_2$O H$_2$O:THF= 1:1	 **2.14o**	36[b] 87

[a] Isolated yield. [b] Yields were determined by ^{1}H NMR spectra. [c] The ratios of *syn:anti* will be discussed in Chapter3.
[d] Only *syn* isomer was obtained.

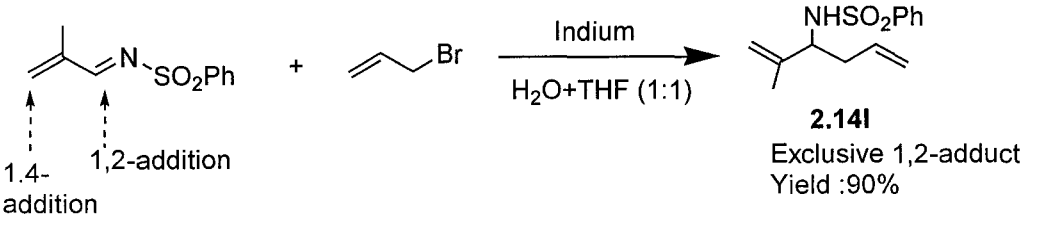
2.2.3 Regioselectivity

The issue of regioselectivity arises when substituted allyl bromide are employed in the reaction. Indium-mediated aqueous allylation reaction of sulfonimines showed excellent regioselectivity when crotyl- (**2.13b**), cinnamyl- (**2.13c**) or γ,γ-dimethylallyl- (**2.13d**) bromides were used. The γ-allylation products were obtained exclusively from the allylation and no α-adducts were observed (Scheme 2.13). These results are in accord with the previously known regioselectivity observed for indium-mediated allylation reaction of carbonyl compounds.[18]



Scheme 2.13

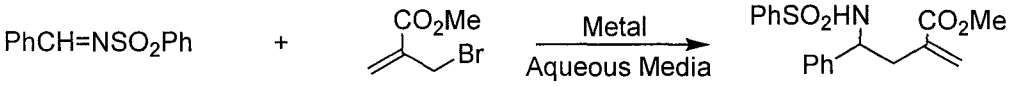
High regioselectivity was also observed when α, β-unsaturated sulfonimines were employed. Only 1,2-adducts were obtained and no 1,4-allylation was observed in the reactions (Table 2.1, *entries* 10, 12, 13) (Scheme 2.14).



Scheme 2.14

2.3 Allylation of Sulfonimines Mediated by Zinc

Similar allylation of sulfonimines in aqueous media mediated by zinc was also investigated. Zinc, unlike indium and tin, may mediate the coupling reaction through a different mechanism.[19] It is interesting to find that, using zinc, the aqueous allylation reaction was relatively accelerated (Table 2.2). The reaction was usually finished in 2 hr to give high yields of the products. Consequently, for the less reactive sulfonimines such as aliphatic sulfonimines or for the less reactive bromides, the zinc-mediated aqueous conditions were preferable to that of indium (Table 2.4 *entries* 5-10). An illustrative example was the reaction of the benzenesulfonimine **2.12a** with methyl 2-(bromomethyl)acrylate. (**2.13f**). Using indium, this reaction gave products derived mainly from the hydrolysis of bezenesulfonimine due to the relatively lower reactivity of the bromide (Table 2.1, *entry* 8). However, when the same reaction was mediated by zinc, the reaction proceeded smoothly in aqueous saturated NH_4Cl solution to give high yield of the product. (Scheme 2.15).



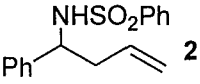
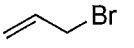
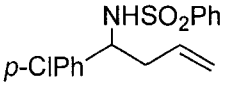
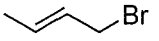
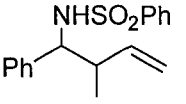
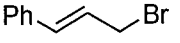
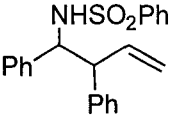
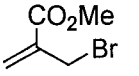
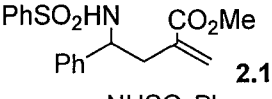
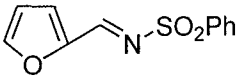
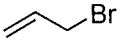
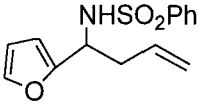
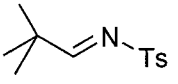
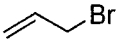
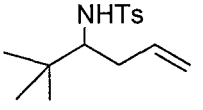
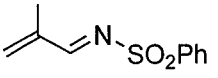
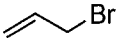
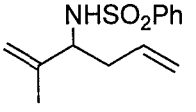
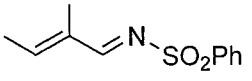
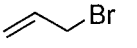
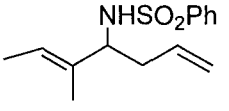
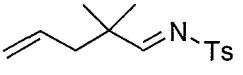
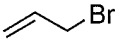
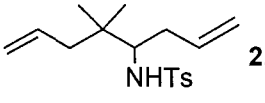
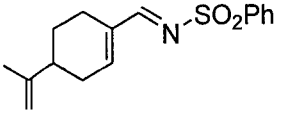
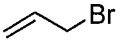
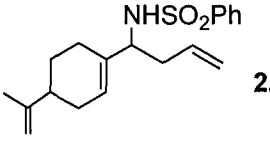
2.13f **2.14h**

	Yield (%)
Indium	30
Zinc	96

Scheme 2.15

Similar to the indium-mediated allylation of sulfonimines, the reaction showed good regioselectivity giving exclusively 1,2-adducts (Table 2.4, *entries 8,9,11*).

Table 2.4 Zinc Mediated Allylation Reaction with Sulfonimines

Entry	Sulfonimine	Allyl Bromide	Product	Yield%[a]
1	$PhCH{=}NSO_2Ph$		 **2.14a**	99[b]
2	*p*-ClPhCH=NSO_2Ph		 **2.14b**	95
3	$PhCH{=}NSO_2Ph$		 **2.14d**	92[c]
4	$PhCH{=}NSO_2Ph$		 **2.14e**	80[d]
5	$PhCH{=}NSO_2Ph$		 **2.14h**	96
6			 **2.14i**	97
7			 **2.14k**	72
8			 **2.14l**	90
9			 **2.14m**	92
10			 **2.14n**	95
11			 **2.14o**	80

[a] Isolated yield. [b] Yields were determined by ^1H NMR spectra.[c] The ratio of syn:anti is 46:54.
[d] Only *syn* isomer was obtained.

2.4 Conclusion

The aqueous metal-mediated Barbier-type organometallic reaction was expanded successfully to C=N electrophiles by using sulfonyl activated aldimines. We have found that sulfonimines can be effectively allylated with either indium or zinc and allyl bromide to give the corresponding homoallylic sulfonamides. The solvents used can be pure water, organic or mixed aqueous organic solvents. When substituted allylic bromides were used, the reaction was found to be regioselective.

2.5 Experimental Section

General Aspect. Chemicals were purchased from Aldrich. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plastic-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5g) and ceric sulfate (1g) in concentrated H_2SO_4/H_2O (10ml/90ml) and heated with a heat gun. Solvents were reagent grade unless otherwise specified. Indium and zinc powder were freshly opened for use. Allyl bromide compounds were checked for purity by ^1H NMR and were distillated or recrystalized if impure.

All nuclear magnetic resonance spectroscopy were carried out on the following apparatus. The ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) were recorded on the Varian Gemini 200 and Mercury 200. The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) were recorded on the Varian Mercury 300 or 400. The ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded on the Varian Unity 500. The chemical shifts are reported on the δ scales in parts per million (ppm) relative to $CDCl_3$ at δ 7.24

ppm for ^{1}H and δ 77.0 ppm for ^{13}C. Singlet (s), doubles (d), triplet (t), quartet (q), broad peak (br) were recorded at the center of the peaks and were used throughout. Melting points are uncorrected. Specific rotations were determined with a Jasco DIP-140 digital polarimeter at 20 °C. The infra-red spectra were carried out on the Bruker IFS48 (neat compound on NaCl plate).

General procedures for the preparation of sulfonimines

Method A

a) **General procedure for the preparation of diethoxymethyl-benzene (2.22).** To a 25 mL round bottom flask, benzaldehyde (5.3g, 50 mmol) and ethyl orthoformate (15 mL, as both reactant and solvent) were added. The mixture was stirred under argon at 0 °C. Then 1N ethereal HCl solution (1 mL) was added slowly via syringe. The reaction was stirred over night at room temperature. Pure diethoxymethylbenzene was obtained by vacuum distillation (70~74 °C/8 mmHg).

b) **Conversion of acetal to benzenesulfonimine (2.12a):** Benzenesulfonamide (1.57 g, 10 mmol) and diethoxymethylbenzene (1.80g, 10 mmol) were mixed together in a 10 mL round bottom flask and heated up to 150 °C until there was no ethanol released. Then the mixture was put under vacuum to cool down. Pure benzenesulfonimine was obtained by recrystalization (methylene chloride and hexane).

Method B

A solution of methacrolein (1.40g, 20.0 mmol) in dichloromethane (100 mL) was cooled to 0 °C under argon and treated with triethylamine (6.07 g, 8.35 mL, 60mmol, 3 eq.) and benzenesulfonamide (3.14g, 20.0 mmol, 1.0 eq.). Titanium tetrachloride (2.08g, 11.0 mmol, 0.55 eq.) was added dropwise to the solution. The mixture was stirred for 30 min at 0 °C. The titanium salt was removed by filtration of the reaction mixture through Celite. The Celite pad was washed by dichloromethane (100 mL) and the combined filtrates were concentrated in vacuum to provide the crude product as clear oil. Further recrystalization (dichloromethane and hexane) offers pure product as crystalline compound (**2.12g**).

Method C

A suspension of tellurium metal (0.070 g, 0.55 mmol) and anhydrous chloramines-T (0.24 g, 1.055 mmol) in toluene (5 mL) was heated at reflux for 1h, at which time the suspension became gray. The aldehyde (1.0 mmol) was added and heating continued for 1h. Methylene chloride was added and the mixture was filtered through Celite. Removal of solvent in vacuum gave the N-tosylimine (**2.12f, 2.12i**) suitable for further use.

General Procedure for Allylation of Sulfonimines

(A) Allylation of sulfonimines mediated by indium

To a stirred mixture of the sulfonimine (**2.12**, 0.5mmol) and allyl bromide (**2.13**, 1.5 mmol) in aqueous or organic solvent (4 mL), indium (1.5mmol) powder was added. The reaction was stirred over night and was quenched by adding 1N HCl (2 mL) and extracted with ether (2 × 15 mL). The combined organic phase was washed with

saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. The crude product, after evaporation of ether, was purified by flash column chromatography on silica gel (eluent: 10~15% ethyl acetate in hexane).

(B) Allylation of sulfonimines mediated by zinc.

To a vigorously stirred mixture of the sulfonimine (**2.12**, 0.5mmol) and allyl bromide (**2.13**, 1.5 mmol) in saturated NH_4Cl aqueous solution (4 mL), was added zinc (1.5mmol) powder. The reaction was stirred for 2 hr and was quenched by adding 1N HCl (2 mL) and extracted with ether (2 × 15 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous Na_2SO_4. The crude product, after evaporation of ether, was purified by flash column chromatography on silica gel (eluent: 10~15% ethyl acetate in hexane).

N-**(1-Phenyl-3-butenyl)benzenesulfonamide (2.14a)** white solid; mp 80-81 °C; IR (neat, cm^{-1}) 3279, 1448, 1323, 1161; ^1H NMR (200 MHz, $CDCl_3$) 7.78-7.63 (m, 2H), 7.50-7.25 (m, 4H), 7.18-7.03 (m, 4H), 5.64 (ddt, 1H, J = 17.5, 9.6, 7.1 Hz), 5.15-4.94 (m, 2H), 5.03 (br 1H), 4.42 (dt, 1H, J = 6.7, 6.7 Hz), 2.47 (dd, 2H, J = 7.0, 7.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 140.6, 140.3, 133.3, 132.5, 129.0, 128.7, 127.8, 127,4, 126,8, 119.7, 58.4, 43.2; MS (CI, NH_3) *m/e* 288 ($M + H^+$, 1), 246 (100); HRMS calcd for $C_{16}H_{17}NO_2S + H^+$ 288.1058, found 288.1059. Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.77; H, 6.36; N, 4.87.

N-**[1-(4-Chlorophenyl)-3-butenyl)benzenesulfonamide (2.14b):** white solid; mp 108-110 °C; IR (neat, cm^{-1}) 3252, 1453,1318, 1162; ^1H NMR (500 MHz, $CDCl_3$) 7.65-7.64 (m, 2H), 7.51-7.48 (m, 1H), 7.38-7.35 (m, 2H), 7.12 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J =

8.5 Hz), 5.52-5.44 (ddt, 1H, J = 17.0, 10.5, 7.0 Hz), 5.10-5.05 (m, 2H), 4.95 (d, 1H, J = 6.5 Hz), 4.38 (dt, 1H, J = 7.0, 7.0 Hz), 2.41 (dd, 2H, J = 7.0, 7.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 140.1, 138.5, 133.1, 132.4, 132.3, 128.6, 128.3, 127.8, 126.9, 119.7, 56.3, 41.6; MS (CI, NH_3) *m/e* 322 (M + H^+, 31), 165 (98), 136 (100); HRMS calcd for $C_{16}H_{16}ClNO_2S$ + H^+ 322.0669, found 322.0667. Anal. Calcd for $C_{16}H_{16}ClNO_2S$: C, 59.71; H, 5.01; N, 4.35. Found: C, 59.54; H, 5.28; N, 4.31.

N-**[1-(4-Methoxyphenyl)-3-butenyl)benzenesulfonamide (2.14c):** white solid; mp 71-73 °C; IR (neat, cm^{-1}) 3279,1612, 1447, 1322,1157; ^{1}H NMR (500 MHz, $CDCl_3$) 7.66-7.47(m, 1H), 7.54-7.32 (m, 3H), 6.97 (d, 2H, J = 8.5 Hz), 6.69 (d, 2H, J = 8.5 Hz), 5.65-5.42 (ddt, 1H, J = 17.4, 9.9, 6.8 Hz), 5.07-5.04 (m, 2H), 4.80 (br, 1H), 4.36 (dt, 1H, J = 6.8, 6.8 Hz), 3.76 (s, 3H), 2.46 (ddd, 2H, J = 6.9, 6.9, 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 158.7, 140.34, 133, 132.1, 132, 128.5, 127.6, 126.9, 119.1, 113.6, 56.5, 55, 41.7; MS (FAB, NaCl) *m/e* 340 (M + Na^+, 4), 276 (82), 161(100); HRMS calcd for $C_{17}H_{19}NO_3S$ + Na^+ 340.0983, found 340.0984. Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.53; H, 6.44; N, 4.90.

N-**(1-Phenyl-2-methyl-3-butenyl)benzenesulfonamide(2.14d):** white solid; mp 128-130 °C; IR (neat, cm^{-1}) 3264, 1450, 1319, 1163; ^{1}H NMR (500 MHz, $CDCl_3$) *syn* isomer 7.60-7.58 (m, 1H), 7.42-7.36 (m, 1H), 7.28-7.24 (m, 3H), 7.13-7.08 (m, 3H), 6.93-6.89(m, 2H), 5.48-5.41 (ddd, 1H, J = 17.5,10.0, 8.0 Hz), 5.40-5.05 (m, 2H), 4.95 (d, 1H, J = 8.0 Hz), 4.30 (dd, 1H, J = 8.0, 5.8 Hz), 2.58-2.50 (m, 1H), 0.93 (d, 3H, J = 7.0 Hz); *anti* isomer 7.55-7.52 (m, 1H), 7.40-7.36 (m, 1H), 7.28-7.24 (m, 3H), 7.13-7.08 (m, 3H), 7.03-6.99 (m, 2H), 5.62-5.54 (ddd, 1H, J = 17.5, 10.5, 8.5 Hz), 5.18-5.12 (m, 2H), 4.98 (d, 1H, J = 8.0 Hz), 4.10 (dd, 1H, J = 8.0, 5.5 Hz), 2.44-2.38 (m, 1H), 0.83 (d, 3H, J = 7.0

Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 140.3, 138.4 (*anti* 139.1), 137.8, 132.0, 131.9, 128.4, 128.3, 127.9, 127.7, 127.2, 127, 126.9, 126.7, 116.9 (117.5), 0.61.4 (61.9), 43.7(44.4), 16.1(16.8); MS (FAB + NaCl) *m/e* 324 ($M + Na^+$, 9.6), 301 (M, 0.6), 246 (78), 145 (100); HRMS calcd for $C_{17}H_{19}NO_2S + Na^+$ 324.1034, found 324.1033. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.75; H, 6.84; N, 4.61.

N-**(1,2-Diphenyl-3-butenyl)benzenesulfonamide (2.14e):** white solid; mp 140-142 °C; IR (neat, cm^{-1}) 3265, 1450, 1320, 1162; ^1H NMR (200 MHz, $CDCl_3$) 7.52-6.82 (m, 15H); 5.85-5.60 (ddd, 1H, J = 18.6, 10.2, 8.3 Hz), 5.06-4.82 (m, 2H), 4.83 (d, 1H, J = 6.0 Hz), 4.58 (dd, 1H, J = 7.5, 6.0 Hz), 3.55 (dd, 1H, J = 8.0, 8.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 140.2, 139.1, 138.3, 136.5, 132.4, 129.1, 128.8, 128.7, 128.2, 128.1, 127.8, 127.7, 127.7, 127.4, 118.7, 62.7, 57.6; MS (CI, NH_3) *m/e* 364 ($M + H^+$, 5), 246 (100); HRMS calcd for $C_{22}H_{21}NO_2S + H^+$ 364.1371, found 364.1371. Anal. Calcd for $C_{22}H_{21}NO_2S$: C, 72.70; H, 5.82; N, 3.85. Found: C, 72.68; H, 6.26; N, 3.84.

N-**(1-Phenyl-2,2-dimethyl-3-butenyl)benzenesulfonamide (2.14f):** white solid; mp 119-120 °C; IR (neat, cm^{-1}) 3276, 1446, 1317, 1160; ^1H NMR (500 MHz, $CDCl_3$) 7.50-7.52 (m, 2H), 7.40-7.39 (m, 1H), 7.26-7.23 (m, 3H), 7.04-7.01 (m, 2H), 6.86-6.84 (m, 2H), 5.56 (dd, 1H, J = 18.0, 11.0 Hz), 5.17-5.06 (m, 2H), 4.93 (d, 1H, J = 7.5 Hz), 4.07 (d, 1H, J = 7.0 Hz), 1.05 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 161.84, 142.46, 139.85, 135.84, 132.9, 132.0, 129.5, 128.4, 127.5, 126.8, 123.4, 115.5, 64.8, 40.8, 24.7; MS (CI, NH_3) *m/e* 316 ($M + H^+$, 4.3), 246 (100); HRMS calcd for $C_{18}H_{21}NO_2S + H^+$ 316.1371, found 316.1371. Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.63; H, 7.05; N, 4.46.

N-(1-Phenyl-3-methyl-3-butenyl)benzenesulfonamide (2.14g): white solid; mp 72-74 °C; IR (neat, cm^{-1}) 3281, 1448, 1323, 1161; ^1H NMR (200 MHz, $CDCl_3$) 7.65-7.62 (m, 2H), 7.50-7.25 (m, 3H), 7.20-7.07 (m, 5H), 4.98-4.48 (br 1H), 4.84 (s, 1H), 4,75 (s, 1H), 4.47-4.35 (dt, 1H, J = 7.4, 4.8 Hz), 2.36 (d, 2H, J = 7.4 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 141.2, 140.9, 140.3, 128.9, 128.6, 127.8, 127.5, 126.9, 115.7, 56.8, 48.0, 23.1; MS (CI, NH_3) *m/e* 302 (M + H^+, 0.6), 246 (100), 145 (62); HRMS calcd for $C_{17}H_{19}NO_2S$ + H^+ 302.1215, found 302.1216. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. Found: C, 67.73; H, 6.81; N, 4.63.

Methyl ester of α-methylene-γ-[(phenylsulfonyl)amino]benzenebutanoic acid (2.14h): colorless oil; IR (neat, cm^{-1}) 3283, 1716, 1446, 1326, 1160; ^1H NMR (200 MHz, $CDCl_3$) 7.70-7.10 (m, 10H), 6.11 (s, 1H), 5.52 (s, 1H), 5.56-5.53 (br, 1H), 4.61-4.50 (dt, 1H, J = 7.3, 7.3 Hz), 3.71 (s, 3H), 2.65 (d, 2H, J = 7.4 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) 167.5, 140.7, 136.1, 132.4, 129.4, 128.9, 128.7, 127.8, 127.3, 126.7, 59.0, 53.4, 41.7; MS (CI, NH_3) *m/e* 346 (M + H^+, 4.1), 246 (100); HRMS calcd for $C_{18}H_{19}NO_4S$ + H^+ 346.1113, found 346.1112. Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.24; H, 5.45; N, 4.22.

N-[1-(2-Furanyl)-3-butenyl]benzenesulfonamide (2.14i): white solid; mp 61-63 °C; IR (neat, cm^{-1}) 3276, 1447, 1329, 1162, 1094; ^1H NMR (200 MHz, $CDCl_3$) 7.78-7.73 (m, 2H), 7.74-7.40 (m, 3H), 7.13 (d, 1H, J = 1.8 Hz), 6.13-6.10 (dd, 1H, J = 3.2, 1.8 Hz), 5.94 (d, 1H, J = 3.2 Hz), 5.70-5.48 (ddt, 1H, J = 17.8, 9.3, 6.9 Hz), 5.09-5.01(m, 2H), 5.05 (br, 1H), 4.58-4.46 (dt, 1H, J = 6.7, 6.7 Hz), 2.53(m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 151.5, 141.15, 139.82, 131.94, 131.69, 128.17, 126.36, 118.71, 109.63, 106.81, 51.42, 39.52; MS (EI) *m/e* 278 (M + H^+, 0.8), 236 (100), 141 (44); HRMS calcd for

$C_{14}H_{15}NO_3S + H^+$ 278.0851, found 278.0851. Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.96; H, 5.43; N, 4.99.

N-**[1-(2-Phenylethenyl)-3-butenyl]benzenesulfonamide (2.14j):** colorless oil; IR(neat, cm^{-1}) 3278, 1642, 1447, 1326, 1162; ^1H NMR (500 MHz, $CDCl_3$) 7.92-7.82 (m, 2H), 7.58-7.40 (m, 3H), 7.40-7.08 (m, 5H), 6.33 (d, 1H, J = 16.0 Hz), 5.83 (dd, 1H, J = 16.0, 6.9 Hz), 5.75-5.54 (m, 1H), 5.12-5.04 (m, 2H), 4.84 (d, 1H, J = 7.3 Hz), 4.14-4.01(m, 1H), 2.33 (dd, 2H, J = 6.9, 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 140.8, 135.9, 132.6, 132.3, 131.5, 128.8, 128.3, 128.11, 127.6, 127.1, 126.2, 119.3, 55.1, 40.0; MS (FAB, NBA + NaCl) *m/e* 336 (M + Na^+, 3.8), 313 (M^+, 0.8), 77 (100); HRMS calcd for $C_{18}H_{19}NO_2S + Na^+$ 336.1034, found 336.1034. Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 68,87; H, 6.35; N, 4.93.

N-**[3-(5, 5-Dimethyl-1-hexenyl)]-p-tolylsulfonamide (2.14k):** white solid; mp 122-124 °C; IR (neat, cm^{-1}) 3287, 2972, 1427, 1323, 1157; ^1H NMR (200 MHz, $CDCl_3$) 7.73 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 5.55-5.34 (m, 1H), 4.88-4.76 (m, 2H), 4.49 (d, 1H, J = 8.0 Hz), 3.19-3.08 (ddd, 1H, J = 8.1, 5.1, 4.4 Hz), 2.42 (s, 3H), 2.32-2.20 (m, 1H), 2.06-1.90 (m, 1H), 0.86 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 143.1, 139.1, 135.3, 129.7, 127.5, 117.9, 63.6, 37.4, 36.6, 28.4, 23.1; MS (CI, NH_3) *m/e* 282 (M + H^+, 60), 240(100); HRMS calcd for $C_{15}H_{23}NO_2S + H^+$ 282.1528, found 282.1527. Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98. Found: C, 64.48; H, 8.59; N, 5.05.

N-**[3-(2-Methyl-1,5-hexadienyl)]benzenesulfonamide (2.14l):** white solid; mp 80-82 °C; IR (neat, cm^{-1}) 3275, 1648, 1449, 1308, 1161; ^1H NMR (200 MHz, $CDCl_3$) 7.87-7.82 (m, 2H), 7.53-7.48 (m, 3H), 5.62-5.41 (ddt, 1H, J = 15.5, 14.0, 7.0 Hz), 5.08-4.98 (m,

2H), 4.80 (s, 1H), 4.77 (s, 1H), 6.20 (d, 1H, J = 6.8 Hz), 3.83-3.74 (dd, 1H, J = 6.9, 6.9 Hz), 2.36-2.12 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 143.1, 140.8, 133.3, 132.8, 129.1, 127.5, 119.3, 113.9, 59.6, 39.6, 19.8; MS (CI/NH_3) *m/e* 252 (M + H^+, 16), 210 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ + H^+ 252.1058, found 252.1059. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.42; H, 7.03; N, 5.64.

N-[4-(5-Methyl-1,5-heptadienyl)]benzenesulfonamide (2.14m): white solid; mp 71-73 °C; IR (neat, cm^{-1}) 3279, 1448, 1325, 1161; ^{1}H NMR (200 MHz, $CDCl_3$) 7.83-7.78 (m, 2H), 7.58-7.38 (m, 3H), 5.65-5.43 (ddt, 1H, J = 17.5, 9.6, 7.0 Hz), 5.34-5.21 (m, 1H), 5.07-5.05 (m, 2H), 4.69 (d, 1H, J = 6.2 Hz), 3.81-3.71 (m, 1H), 2.34-2.09 (m, 2H), 1.37 (d, 3H, J = 6.7 Hz), 1.26 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 141.0, 133.9, 133.2, 132.5, 128.9, 127.7, 123.5, 118.7, 61.8, 39.7; MS (CI/NH_3) *m/e* 266 (M + H^+, 8.8), 224 (100); HRMS calcd for $C_{14}H_{19}NO_2S$ + H^+ 266.1215, found 266.1215. Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.69; H, 7.50; N, 5.34.

N-[4-(5,5-Dimethyl-1,7-octadienyl)]-*p*-tolylsulfonamide (2.14n): white solid; mp 59-60 °C; IR (neat, cm^{-1}) 3288, 2970, 1431, 1323, 1158; ^{1}H NMR (200 MHz, $CDCl_3$) 7.72 (d, 2H, J = 8.1 Hz), 7.27 (d, 2H, J = 8.1 Hz), 5.90-5.69 (ddt, 1H, J = 16.9,14.3,11.4 Hz), 5.53-5.32 (ddt, 1H, J = 17.2, 9.9, 6.9 Hz), 5.07-4.95 (m, 2H), 4.86-4.74 (m, 2H), 4.41 (d, 1H, J = 9.6 Hz), 3.26-3.15 (ddd, 1H, J = 9.2, 5.1, 4.1 Hz), 2.41 (s, 3H), 2.34-2.21 (m, 1H), 2.00 (d, 2H, J = 7.3 Hz), 2.06-1.91 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 143.1, 139.2, 135.2, 134.83, 129.7, 127.5, 118.1, 118.0, 62.7, 45.2, 39.4, 37.1, 26.0, 25.4, 23.1; MS (CI/NH_3) *m/e* 308(M + H^+, 49.4), 266(91), 224 (100); HRMS calcd for $C_{17}H_{25}NO_2S$ + H^+ 308.1684, found 308.1686. Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.21; H, 8.61; N, 4.69.

1R-N-[1-[4S-(2-propenyl)cyclohexenyl]-3-butenyl]benzenesulfonamide and 1S-N-[1-[4S-(2-propenyl)cyclohexenyl]-3-butenyl]benzenesulfonamide (2.14o): white solid; mp 75-76 °C, de = 51% (determined by ^{13}C NMR, the absolute configuration was not assigned); IR (neat, cm^{-1}) 3276, 2921, 1447, 1323, 1160; ^{1}H NMR (200 MHz, $CDCl_3$) 7.86-7.82 (m, 2H), 7.63-7.41 (m, 3H), 5.66-5.42 (m, 1H), 5.51-5.45 (m, 1H), 5.12-4.86 (m, 2H), 4.86 (br, 1H), 4.70-4.52 (m, 2H), 3.86-3.76 (m, 2H), 2.37-2.10 (m, 2H), 1.65 (s, 3H), 1.48-1.98 (m, 6H), 1.40-1.25 (m, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) (the ^{13}C NMR signals in parentheses are from two diasteroisomers) 149.4, 141.2, 134.8, 133.9 (133.7), 132.6 (132.5), 129.0, 127.8 (127.7), 125.2(126.1), 118.8, 109.2, 60.2(60.3), 41.8(42.3), 39.7 (39.3), 31.7 (31.8), 28.4 (28.3), 25.6 (25.3), 22.3; MS (FAB, NBA + NaCl) *m/e* 354 ($M + Na^+$, 9), 175 (74), 77 (100); HRMS calcd for $C_{19}H_{25}NO_2S + Na^+$ 354.1504, found 354.1504. Anal. Calcd for $C_{19}H_{25}NO_2S$: C, 68.85; H, 7.60; N, 4.23. Found: C, 68.59; H, 7.91; N, 4.25.

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Chapter 3

The Barbier-type Allylindation of Sulfonimines. The Issue of Stereocontrol in Aqueous Media

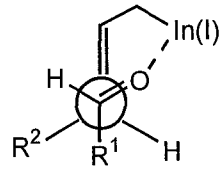
3.1 Introduction

A reliable synthetic methodology should always be based on the corner stone of a clear understanding of its mechanism and its stereochemistry. The discovery of the allylindation reaction in aqueous media has provoked increasing interest in the scrutiny and application of this methodology in organic synthesis.[1] This exploration of aqueous allylindation reaction not only leads to a better understanding of its mechanism but also to an attempt to rationalize its stereochemistry, which carries important implication for the use of allylindium reagents in the construction of stereochemically well-defined molecules.[2] Moreover, it also provides us an opportunity to examine the issue of stereocontrol in aqueous media, which cannot be done for most other allylmetal reagents because of their instability in water.

In the earlier chapter, the aqueous allylation of sulfonimines was successfully conducted. Concerning the stereochemistry of this reaction, the use of sulfonimines not only provided a useful methodology for allylindation of C=N electrophiles in aqueous media, but also provided an ideal model for the comparison of stereochemical behaviors between carbonyl compounds and C=N electrophiles. In this chapter, we will engage in a careful examination of the stereochemistry of the aqueous allylindation of sulfonimines.

3.2 Diastereoselectivity in the Reaction with γ-Substituted Allylic bromides. The Insight of the Transition State from the Solvent Effect

A basic but important stereochemistry issue arises when γ-substituted allylic bromides are employed in the reaction, giving products with two contiguous stereogenic centers. To understand the diastereoselectivity of the reaction, it is essential to elucidate the mechanism of the reaction. Recently, the nature of the allylindium intermediate has been clarified as allylindium(I) in the aqueous indium-mediated allylation reaction.[3] On the other hand, it has also been suggested that the transition state in the reaction of the allylmetal with C=O compounds is represented by the *synclinal* model due to the chelating interaction between oxygen and indium. Such model has been successfully employed to account for the stereochemical outcomes of the aqueous Barbier-type allylation reactions with carbonyl compounds. (Scheme 3.1)

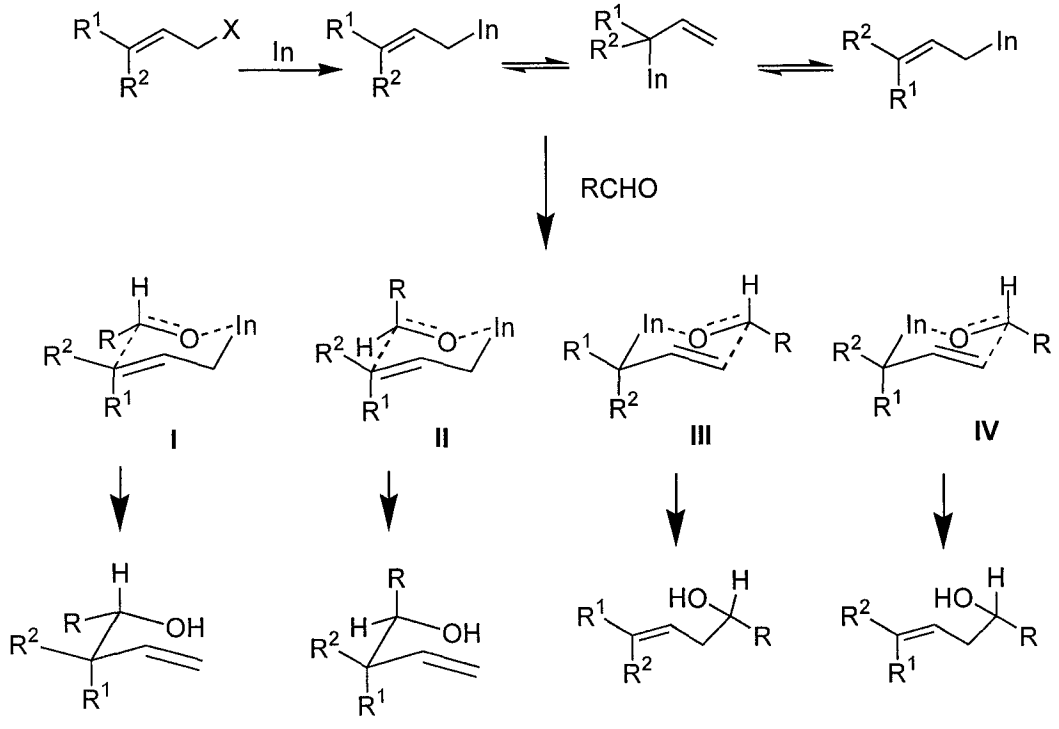


synclinal transition state

Scheme 3.1

Chan and Isaac[4] carefully studied the diastereoselectivity of the aqueous indium-mediated Barbier-type allylation reaction of aldehydes with γ-substituted allyl bromides. They argued that the Zimmerman type transition states could be used to account for the diastereoselectivity of the reaction. (Scheme 3.2) When the substituent (R_1 and R_2) is bulky, the cyclic transition state **III** or **IV** is preferred. Otherwise, for most substituents, transition state **I** or **II** predominates. Apparently the diastereoselectivity should be

governed by the steric size of the substituents both on aldehyde (R) and on the γ-subsitutuent of the starting bromide. In general, the *anti* product would be favored.



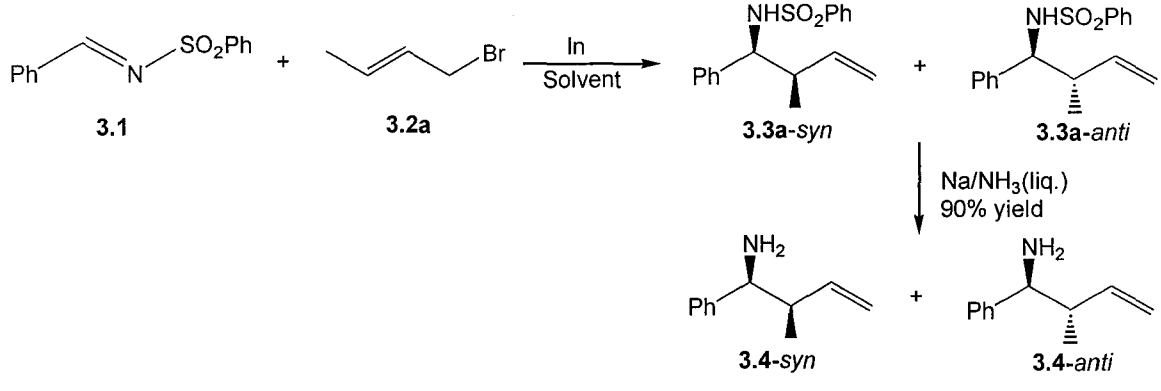
Scheme 3.2

Although C=N electrophiles generally share many similarity with carbonyl electrophiles, they hold their own properties in many aspects including their different nucleophilicity and chelation ability. The first issue in this chapter is to examine if the stereochemistry model we discussed above could also be applied to the C=N electrophiles.

3.2.1 Crotylation Reaction of Benzenesulfonimine

We initiated our study by examining the crotylation reaction of benzenesulfonimine (**3.1**) in mixtures of THF and water with different ratios. The relative configurations of the sulfonamide products were determined by the cleavage of the sulfonyl group by using

sodium in liquid NH_3 at –38°C giving the corresponding primary homoallylic amines, which are known compounds (**3.4**) (Scheme 3.3). It was found that in co-solvent of THF and water, the reaction gave the crotylation product in favor of the *syn* isomer (Table 3.1, *entries 2~8*). The maximum diastereoselectivity (*syn : anti* = 4:1) was obtained when the reaction was conducted in 1:1 ratio of THF and water (*entries 5*). Interestingly, when the reaction was conducted in water alone, reversed diastereoselectivity was found. A slight excess of the *anti* products was obtained with the ratio of *syn* to *anti* at about 1:1.5 (*entry 1*). In comparison, the crotylation of benzaldehyde in water mediated by indium gave a nearly 1:1 ratio of mixture of the *anti* and *syn* isomers.[4]



Scheme 3.3

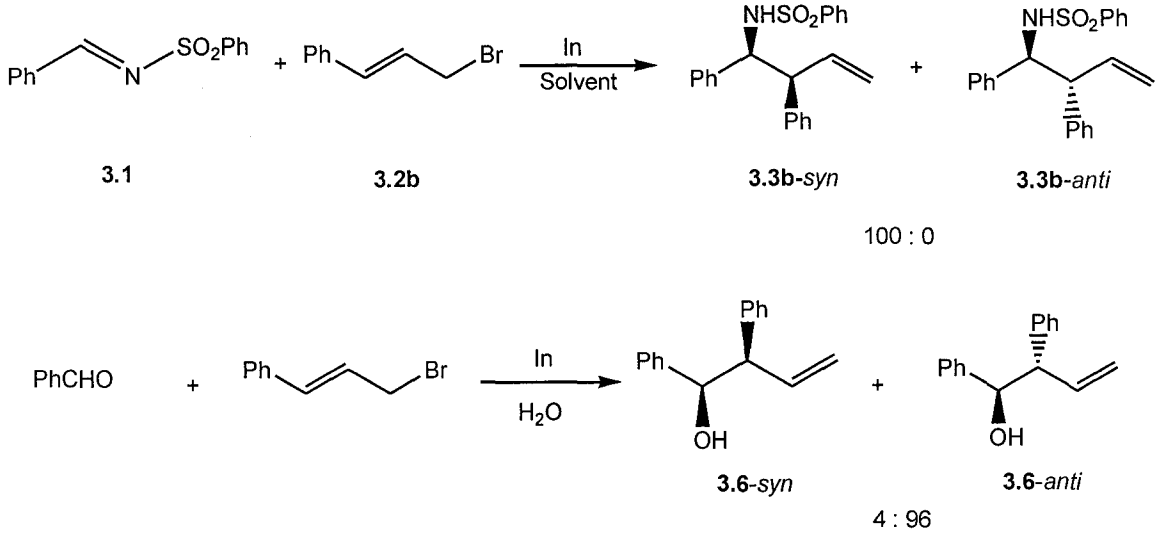
Table 3.1 Reaction of benzenesulfonimine (3.1) with crotyl bromide (3.2a) in different solvents

Entry	Solvent (H_2O:THF)	Yield%[a]	3.3a *syn:anti*
1	100:0	98	39:61
2	95:5	98	66:44
3	90:10	98	67:33
4	70:30	98	78:22
5	50:50	98	79:21
6	40:60	98	78:22
7	30:70	98	77:23
8	0:100	98	68:32

[a] Yields were determined by ^{1}H NMR spectra.

3.2.2. Allylation Reaction of Benzenesulfonimine with Cinnamyl Bromide

In the allylation of benzenesulfonimine (**3.1**) with cinnamyl bromide (**3.2b**) mediated by indium in 1:1 H_2O/THF, the reaction gave only one crystalline compound **3.3b** in high yield. X-ray crystallography showed that the compound had *syn*-stereochemistry.[5] (Figure 3.1) The same *syn*- stereoisomer was obtained, albeit in lower yield, when the reaction was carried out in water alone. The *syn*-selectivity in this case is in contrast with the diastereoselectivity in the indium-mediated allylation of benzaldehyde with cinnamyl bromide in water, in which an *anti*-stereoselectivity was observed (*anti:syn*=96:4).[4]



Scheme 3.4

We have also examined briefly the diastereoselectivity of the zinc-mediated coupling reaction. In the coupling of benzenesulfonimine (**3.1**) with cinnamyl bromide mediated by zinc, the same *syn*-**3.3b** was obtained.

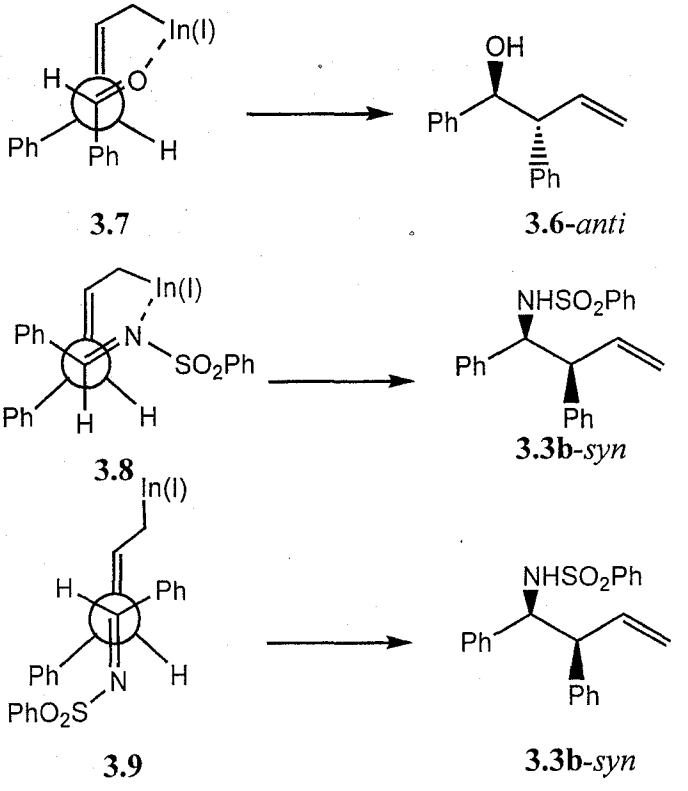
3.2.3 Discussion

The rationalisation of the stereochemistry outcome gave us some insight of the stereo control in the transition state. The explanation should be based on the following considerations.

- With the strong electron-withdrawing sulfonyl group attached to nitrogen, the co-ordination of the nitrogen with indium is weaker than in the case of carbonyl compounds.
- The chelation effect of nitrogen and indium will be further weakened when the reaction was performed in pure water where the indium ion is presumably solvated.
- The sulfonimine are known to have E-configurations in general.

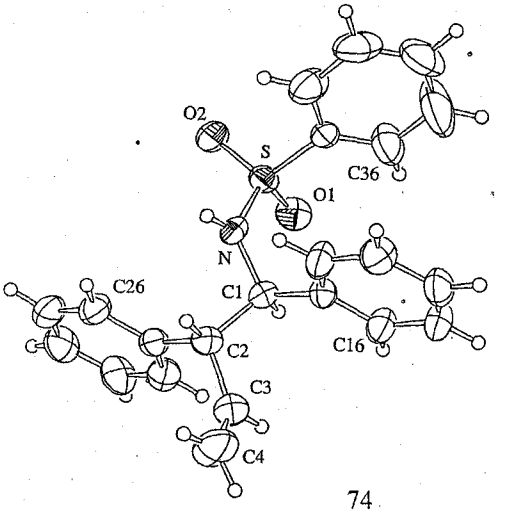
In the indium-mediated allylation reaction in aqueous media, it has been suggested that the reaction proceeds through an allylindium(I) intermediate. Furthermore, the allylindium(I) intermediate has been postulated to react with the carbonyl compound via a six-membered chair transition state.[6] This has been used as the explanation to account for the regio- as well as the diastereoselectivity in the reaction of benzaldehyde with cinnamyl bromide to give compound **3.6** with anti stereochemistry (Scheme 3.5, **3.7** to **3.6**). If the same mechanism is invoked for the reaction between benzenesulfonimine **3.1** and cinnamyl bromide with indium, a transition state such as **3.8** would have to be postulated to accommodate the E-transoid structure of the sulfonimine **3.1**. While this would indeed lead to the formation of the *syn* product **3.3b**, there are considerable gauche interactions in **3.8**. Alternatively, a transition state such as **3.9** with fewer gauche interactions but with anti attack[7] of the allylindium on the electrophilic carbon center can

also lead to the *syn* product **3.3b**. Information available at this time is insufficient for us to draw any definite conclusion. There has been no mechanistic studies regarding the zinc-mediated reaction, and reaction occurring at the metal surface cannot be excluded.[8] It is interesting to note, however, that the same product *syn*-**3.3b** was obtained under the zinc-mediated conditions as in the indium-mediated reaction.

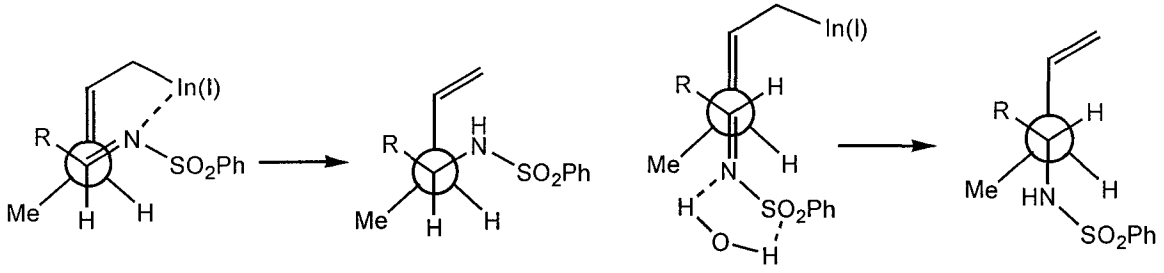


Scheme 3.5

Figure 3.1 X-ray crystallography of compound 3.3b



In the crotyl bromide case, the sensitivity of the diastereoselectivity to solvent composition (Table 3.1) suggests that there may be more than one possible mechanism operating in the reaction between allylindiums with sulfonimines.



3.10 *syn*-**3.3a** **3.11** *anti*-**3.3a**

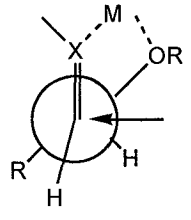
Scheme 3.6

When the reaction was performed in water, co-ordination of water with the sulfonimine function will lead the reaction to undergo non-chelation control giving the *antiperiplanar* transition state (**3.11**) (Scheme 3.6), and therefore giving the preferred formation of the *anti*-**3.3a** product. On the other hand, when the reaction was performed in mixed solvents containing THF, the indium atom was less solvated and the reaction could proceed with *synclinal* transition state **3.10** due to the chelation effect between indium and nitrogen and therefore gave *syn*-**3.3a**. The change from **3.11** to **3.10** can then be used to explain the change in diastereoselectivity as the solvent is changed from water alone to water/THF mixed solvent. It should be noted that in **3.11**, there is considerable steric crowding between R, Me and the nitrogen. If the Me is replaced by a sterically even more demanding group, one would expect the transition state **3.9** (Scheme 3.5) to be favored irrespective of solvent. This is consistent with the previous discussion on the exclusive *syn* selectivity of the cinnamylation of benzenesulfonimine.

3.3 Chelation Effect

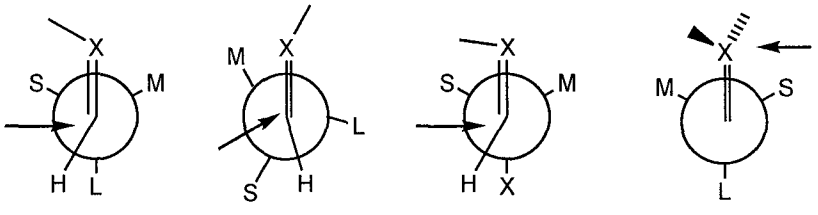
There have been extensive studies on the stereochemistry of nucleophilic attack on C=X facial functions. The stereochemistry of the addition reaction of C=X bond was generally summarized in the chelation or non-chelation models. In the case of chelation control, the degree of freedom of the transition state is reduced by the proximal chelation group and the nucleophile will add from the more accessible side. With the non-chelation model, stereochemical outcome can be predicted by the Cram's rule using the Felkin-Anh, Cornforth, or Yamamoto models.[9] (Scheme 3.7)

Chelation Control:



Cram's 'cyclic' model

Nonchelation Control:

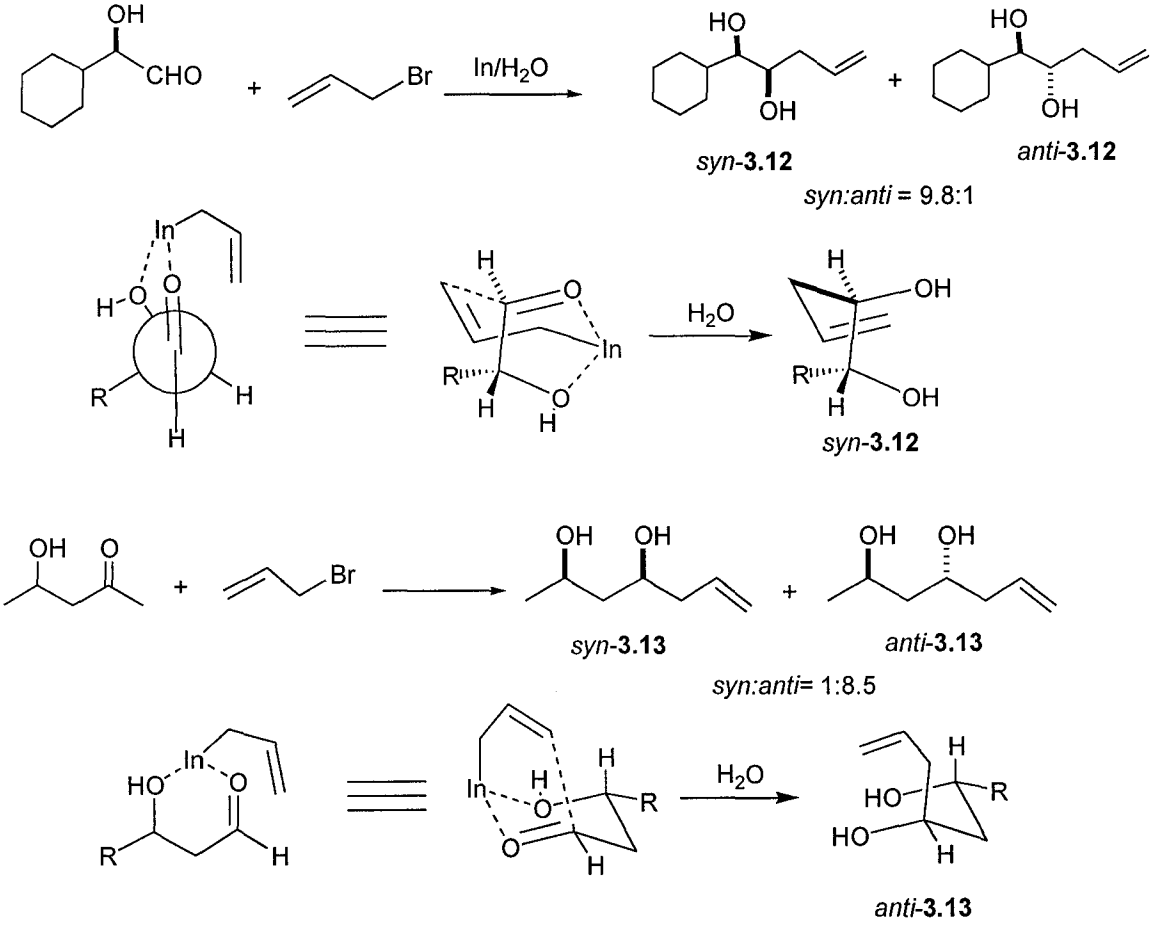


Cram's rule *Felkin-Anh model* *Cornforth model* *Yamamoto model*

Scheme 3.7

Through the extensive research by the Paquette's group, the stereochemistry outcome of allylindation of carbonyl functions has been well interpreted in terms of the involvement of Cram-like transition states. The establishment of this conclusion is based on the series of work from this group on careful examination of the impact of proximal chelating groups either on carbonyl compounds or on allylic bromides towards the diastereoselectivity.[10] For example, with α-hydroxyl substituent presented on aldehydes,

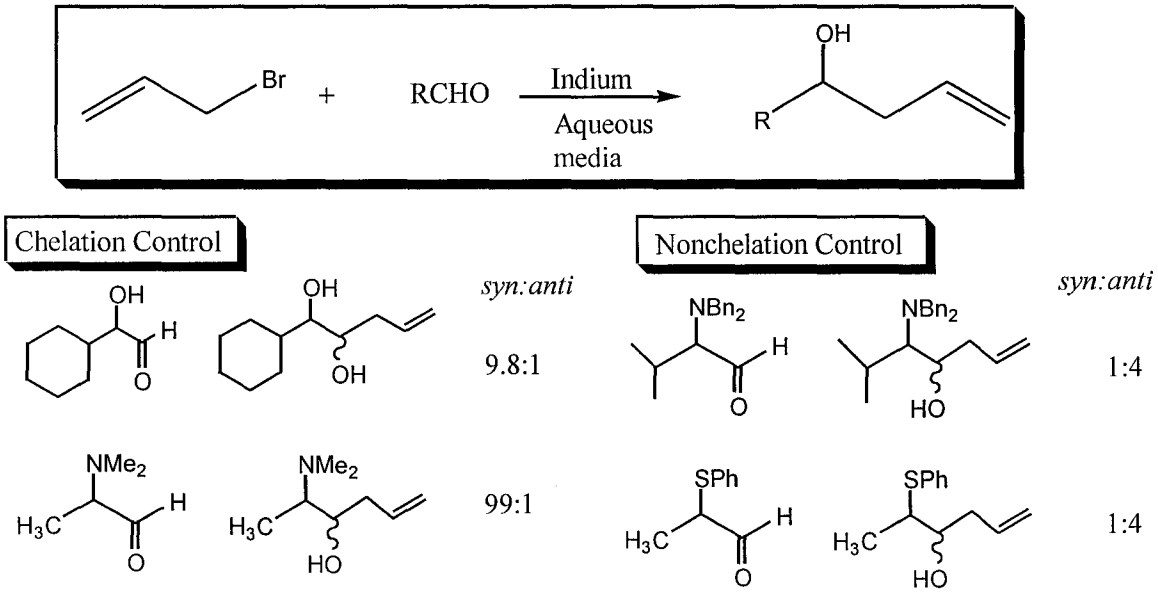
the allylindium intermediate coordinates with both the carbonyl function and the hydroxyl function as in Scheme 3.8 leading to the *syn* adduct **3.12**. Similarly, allylation of β-hydroxyl substituted aldehydes giving preference of *anti*-**3.13** can also be accounted for by the dual coordination of indium with both hydroxyl and carbonyl function. (Scheme 3.8)



Scheme 3.8

However, their study also suggested that there was interesting competition between the chelation control and the sterical impact in the transition state. Slight difference in the substrates such as the size of atom, the strength of the chelation, will give rise to different stereochemical outcome as the examples shown in Scheme 3.9. Therefore, in

our case of using C=N electrophiles, the rationalization of stereochemical results gained in the allylindation of carbonyl compounds is not completely comparable to the stereochemical outcome to the case of aldimines.

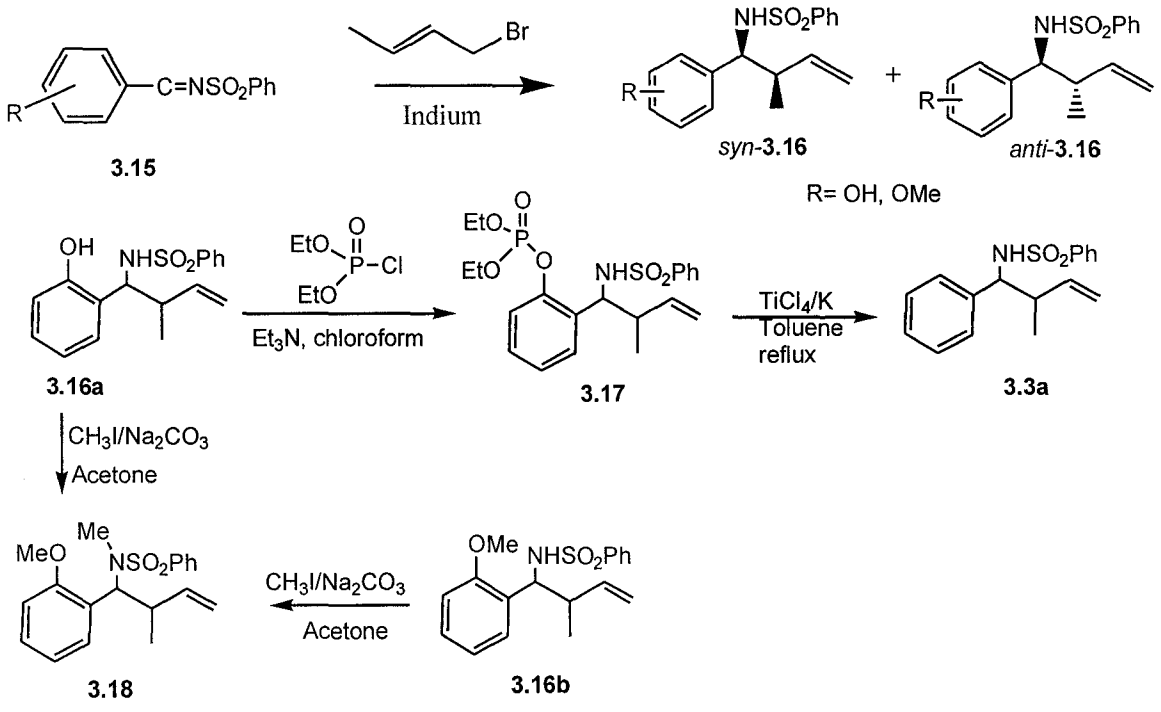


Scheme 3.9

The results showed in the previous sections suggest that the stereochemistry in the crotylation of sulfonimines may be quite sensitive to various factors. We therefore examined the crotylation of a number of sulfonimines, which possess proximal groups capable of chelation in order to probe the influence of the chelating groups on the stereoselectivity. In order to simplify the stereochemical determination, we concentrate at this time on substrates that will give only two contiguous stereo-centers in the final products.

3.3.1 Crotylation of Substituted Benzenesulfonimines[11]

As a convenient way to launch this work, a number of 2-, 3- and 4-OH and OMe substituted benzenesulfonimines (**3.15a~e**) were prepared. They were then reacted with crotyl bromide and indium in water and in water/THF (1:1) to give the substituted sulfonamides **3.16a~e**. In all cases, two diastereomers were formed. Their stereochemistries were correlated to the unsubstituted **3.3a** in the following manner[12] (Scheme 3.10). Compound **3.16a** (as a mixture of two diastereomers) was converted to the phosphate **3.17**. The phosphate group on **3.17** was then reduced to give compound **3.3a**. From the ^{1}H NMR of **3.3a**, the ratio of the two diastereomers can be determined. This was then related to the ratio of the two diastereomers in the original mixture in **3.16a**. There was no loss of stereochemical integrity in the transformations in Scheme 3.9 since different ratios in the starting **3.16a** correlated to the resulting ratios in **3.3a**. The stereochemistry of compound **3.16b** was related to compound **3.16a** through the dimethyl derivative **3.18** according to Scheme 3.9. For compounds **3.16c~e**, the ratios of the diastereoisomers were determined using ^{1}H NMR, with the assumption that the coupling constants for the benzylic protons of the *syn*- isomers are larger than that of the *anti*-isomers in accordance with the pattern observed for **3.18**.

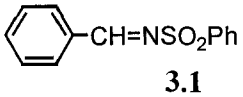
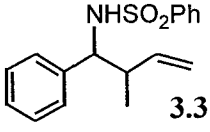
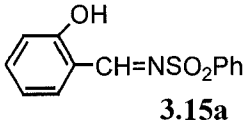
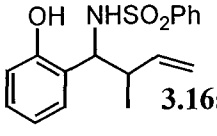
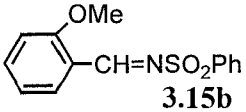
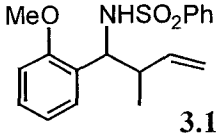
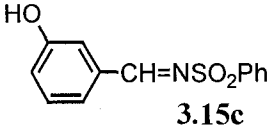
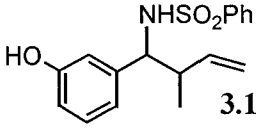
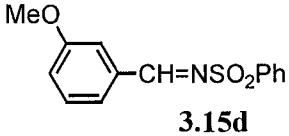
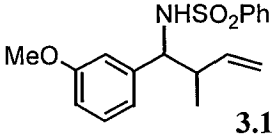
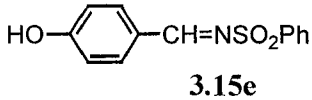
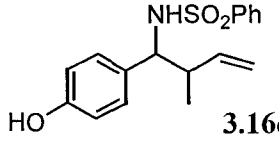


Scheme 3.10

It can be seen from Table 3.2 that similar yields were obtained in the reaction regardless of the substituents on the benzene ring. Interestingly, the *p*-OH substituent showed no effect on the stereoselectivity of the reaction. In water alone, both **3.1** and **3.15e** gave the *anti*-isomers preferentially to nearly the same extent, and the stereoselectivity is reversed to give the *syn*-isomers mainly in water/THF (1:1), also to nearly the same extent. This suggests that electronic effect of the substituent does not play any role in the stereoselectivity of the reaction. On the other hand, the *o*-OH substituted compound **3.15a** gave preferentially the *syn*-isomer irrespective of the solvent systems used (Table 3.2, *entry 2*). Since electronic effect is not involved, the change in pure water may be ascribed to either the steric or the chelation effect of the *o*-OH on the reaction. By comparing the *o*-OH compound **3.15a** with the *o*-OMe compound **3.15b** (Table 3.2, *entry 3*), it seems that the change in stereoselectivity can not be due to steric effect since compound **3.15b** gave the same stereochemical results as compound **3.1.** The change is consistent with the chelation effect of the *o*-OH group, which exists in pure

water as well as in water/THF (1:1) and is diminished on becoming OMe. Compounds **3.15c** with OH at the *meta* position of the benzene ring, showed a small change towards *syn*- selectivity relative to the parent compound **3.1** but less so than compound **3.15a**. The observation is consistent with the expectation that chelation of the *m*-OH with the crotylindium intermediate would be weak due to the strain imposed by the *trans*-cycloheptene-like requirement. With compound **3.15d**, where the *m*-OH was replaced by *m*-OMe, the stereoselectivity was the same as either compound **3.1** or **3.15e**.

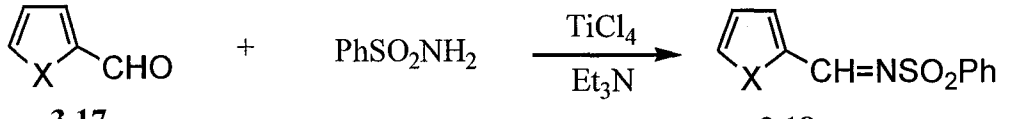
Table 3.2 Crotylation of Substituted Benzenesulfonimines

Entry	Sulfonimines	THF:H_2O	Product	Yield%[a]	*Syn* : *Anti*[b]
1	 **3.1**	0:100	 **3.3**	98[c]	39:61
		50:50		95	79:21
2	 **3.15a**	0:100	 **3.16a**	74[c]	76:24
		50:50		88	77:23
3	 **3.15b**	0:100	 **3.16b**	75	35:65
		50:50		90	62:38
4	 **3.15c**	0:100	 **3.16c**	71[c]	57:43
		50:50		80	74:26
5	 **3.15d**	0:100	 **3.16d**	95	37:63
		50:50		98[c]	81:19
6	 **3.15e**	0:100	 **3.16e**	80	37:63
		50:50		83[c]	78:22

[a] All the reactions are conducted in 0.5 mmol scale. All the yields are isolated yields unless specified. [b] The ratio of syn:anti is determined by ^{1}H NMR spectra of the crude product. [c] The yield was determined by ^{1}H NMR.

3.3.2. Crotylation of Heteroarylaldehyde Sulfonimines

Encouraged by what appeared to be a chelation effect in the aqueous crotylation of *o*-hydroxyl-benzaldehyde sulfonimine **3.15a,** we extended the study to a series of heteroarylaldedyde sulfonimines which were prepared according to Scheme 3.11.



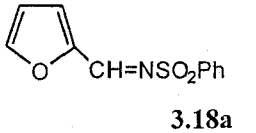
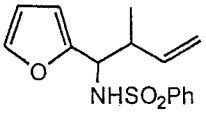
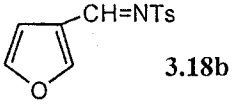
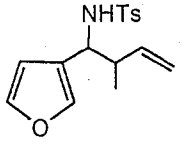
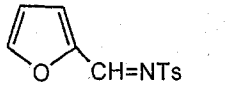
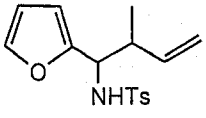
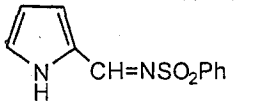
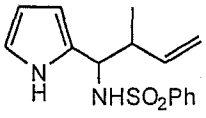
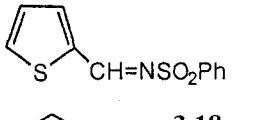
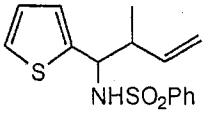
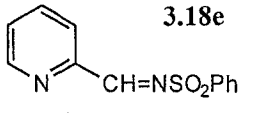
3.17 **3.18**

	yield%
X= O	80
S	84
NH	35

Scheme 3.11

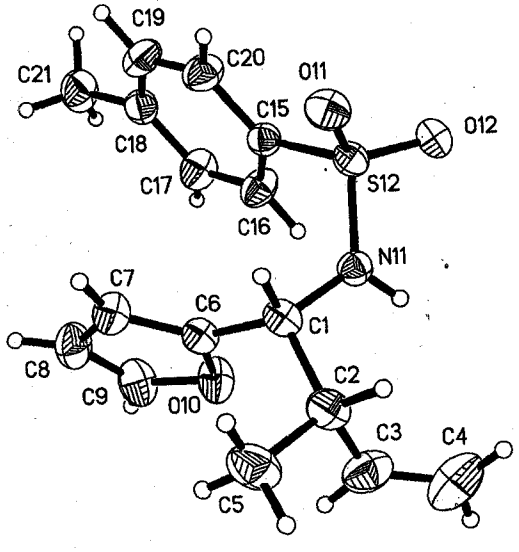
The results are summarized in Table 3.3. In the case of compound **3.18c** (Table 3.3, *entry 3*), the major isomer of the product **3.19c** was obtained as colorless crystals, and its stereochemistry was determined by X-ray crystallography to be the *syn-* isomer.[13] (Figure 3.2) Using this compound as the reference, ^{1}H NMR was used to determine the relative ratios of *syn-* and *anti*-isomers for the other compounds in Table 3.3 (*entries 1-5*). In all cases, *syn-* selectivity was observed, and the selectivity was enhanced as the solvent changed from water alone to a THF:water (1:1) mixed solvent. A selectivity of *syn:anti*=93:7 could be obtained for the furan compound **3.18a** as well as the pyrrole compound **3.18d**. A higher proportion of THF beyond the 1:1 ratio in the solvent did not seem to improve the selectivity further. In the thiophene case (compound **3.18e**), the stereoselectivity was slightly less, though still *syn-* selective. Finally, in the case of the pyridine compound **3.18f** (*entry 6*), crotylation was not successful, because the sulfonimine was hydrolyzed to the aldehyde prior to crotylation.

Table 3.3 Aqueous Allylindation Reaction of Sulfonimines Bearing α–Chelating Groups

Entry	Sulfonimine	Product	Solvent THF:H_2O	Yield%[a]	syn:anti[b]
1	 **3.18a**	 **3.19a**	0:100	90[c]	76:34
			50:50	94	93:7
			10:1	99[c]	93:7
2	 **3.18b**	 **3.19b**	0:100	85[c]	59:41
			50:50	91	86:14
3	 **3.18c**	 **3.19c**	0:100	90[c]	76:34
			50:50	95	93:7[d]
			5:1	99[c]	93:7
4	 **3.18d**	 **3.19d**	0:100	72	68:32
			50:50	80	94:6
5	 **3.18e**	 **3.19e**	0:100	83	57:43
			50:50	92	85:15
6	 **3.18f**	only hydrolyzed products were observed	0:100	0	---
			50:50	0	---

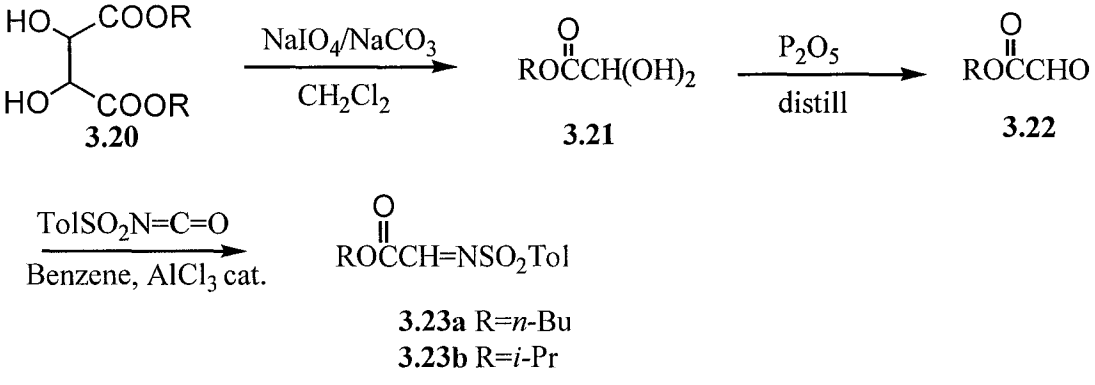
[a] Isolated yields [b] The ratio of *syn:anti* was determined by ^{1}H NMR of the crude product. [c]Yields determined by ^{1}H NMR of the crude product. [d] The relative configuration was determined by single crystal X-ray crystallography.

Figure 3.2 X-ray crystallography of compound 3.19c



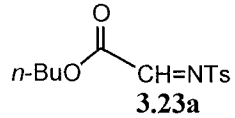
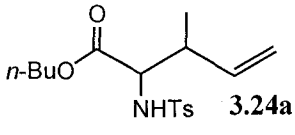
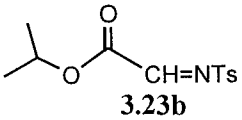
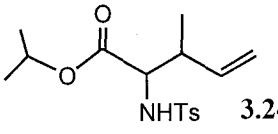
3.3.3. Crotylation of Sulfonimino-acetic Acid Ester

Allylic α-amino acids are quite useful building blocks in organic synthesis because the γ,δ-double bond can easily be transformed into other functionalities.[14] Reactions of various allylic metals with α-imino esters in organic solvents have been used extensively to prepare these allylic α-amino acids.[15] Relatively few reactions were carried out in aqueous media and none with indium.[16] We therefore examined the crotylation of the α-sulfonimino acetic acid esters **3.23a** and **3.23b**, which were prepared according to Scheme 3.12.



Scheme 3.12

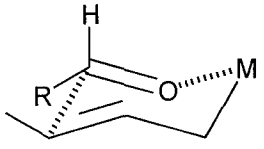
Table 3.4 Aqueous Allylindation Reaction of Sulfonimines Bearing α–Chelating Groups

Entry	Sulfonimine	Product	Solvent THF:H_2O	Yield%[a]	syn:anti[b]
1	 **3.23a**	 **3.24a**	50:50 100:0 0:100	45 56 0	93:7[c] 87:13 ---
2	 **3.23b**	 **3.24b**	50:50 0:100	40 0	95:5[c] ----

[a] Isolated yields [b] The ratio of *syn:anti* was determined by ^{1}H NMR of the crude product. [c] The relative configuration was determined by comparation of the reported compounds data in ref. 15d

The reactions gave moderate yields of the crotylation products (Table 3.4). The stereoselectivity was however high, giving a ratio of *syn:anti* as high as 19:1 in the case of **3.23b**. By comparison, a *syn:anti* ratio of 6-10:1 was obtained in the crotylation of similar α-sulfonylimino-acetic acid esters with *trans*-2-butenyl-tri-n-butylstannane in organic solvents.[14]

3.3.4 Discussion

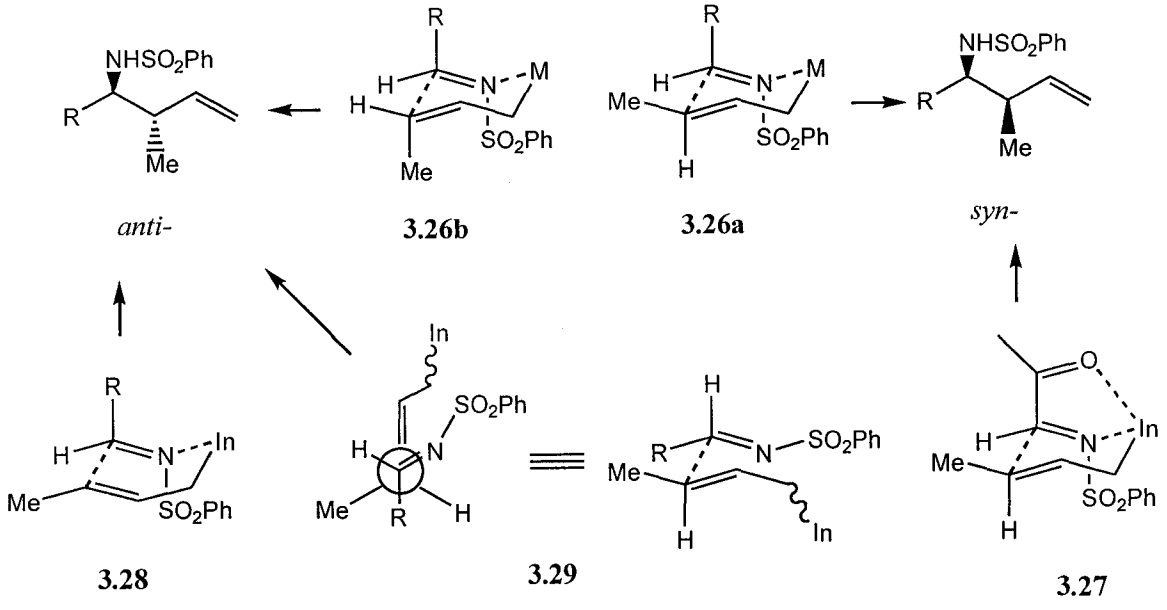


3.25

The diastereoselectivity in the reaction of crotyl metals with carbonyl compounds has been well studied.[17] In general, it is accepted that for crotyl organometals incorporating boron, aluminum, pentavalent silicon and tin (thermal and neutral reaction conditions), they react with aldehydes via chairlike transition states (similar to **3.25**). The stereochemical outcome of the product from C-C bond formation is controlled by the double bond geometry of the starting crotyl organometal.[18] For crotyl metals incorporating lithium, magnesium, or zinc where metallotropic rearrangement of the crotyl metals can occur with isomerization of the double bond geometry, then the stereochemical information of the reagent cannot be transmitted to the product. Crotyl indium is likely to belong to this latter class of crotyl metallic reagents since it has been established that the double bond geometry of the starting bromide has no bearing on the stereochemical outcome of the final product.[19] The reactions of crotyl metals with imines are more complicated, because the imine nitrogen possesses an additional group and the

imines often have E-geometry. If there is coordination between the imino nitrogen with the metal in a chair-like transition state, the groups on the C=N double bond will assume the axial geometry. Depending on the double bond geometry of the crotyl metal, there will be two diastereomeric transition states (**3.26a** and **3.26b**). The *syn*- diastereomer will be formed via the C (E, E) transition state **3.26a** (chair with E-crotyl and E-imine) whereas the *anti*- diastereomer will arise from the energetically less favorable C (Z, E) transition state **3.26b** (chair with Z-crotyl and E-imine). This is presumably what happened in cases where the imine had a proximal chelating group (as in compounds **3.15a**, **3.18a**, **3.18c~e**, **3.23a** and **3.23b**). The C (E, E) transition state structure is reinforced by the additional chelating stabilization as illustrated in **3.27** giving rise to the *syn*- product preferentially irrespective of the solvents used. It is however more difficult to explain the *anti*- selectivity in the non-chelating case (as in compounds **3.1**, **3.15b**, **3.15d** and **3.15e**) because the C (Z, E) transition state **3.26b** is clearly energetically not favorable. In the reactions between crotylboronates and imines, a B (E, E) transition state **3.28** (boat with E-crotyl and E-imine,) has been invoked to account for the selective formation of the *anti*- diastereomer.[20] It is argued that the unfavorable 1,3-diaxial interactions in **3.26b** are relieved in **3.28**. It is not clear whether this is the appropriate explanation for the reaction of crotylindium with benzaldehyde sulfonimine **3.1** (and related compounds with no additional chelation). It would seem that the change from *anti*- to *syn*-selectivity as the solvent changed from water to THF:water mixture cannot be explained on the basis of structure **3.28**. A more plausible explanation is to argue that, in water as solvent, there is no coordination between the indium metal and the imine nitrogen. The crotylindium and imine simply approach each other in the synclinal

transition state **3.29** which minimizes the gauche interactions at the incipient C-C bond. The resulting product would lead to the *anti-* isomer. As the solvent changes from water to a less polar medium with THF, coordination between the indium metal and the imine nitrogen becomes important, and the C (E, E) transition state **3.26a** dominates, leading to more *syn-* stereoisomer.



Scheme 3.13

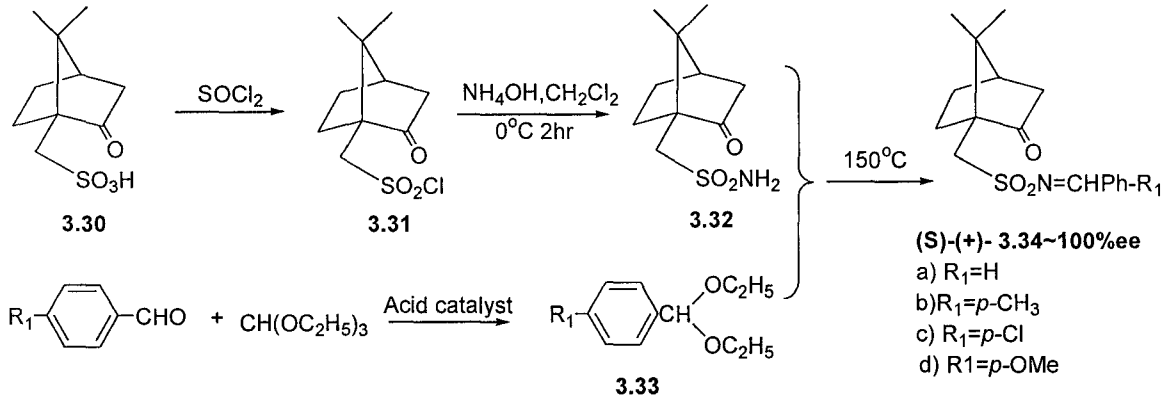
3.4 Asymmetric Allylation Reaction of Chiral Sulfonimines and Sulfinimine

By using sulfonimines instead of regular aldimines, the metal-mediated aqueous allylation reaction to C=N electrophiles can be smoothly carried out in aqueous media. Moreover, the diastereo-selectivity of the aqueous Barbier-type allylation reaction of sulfonimines has also been carefully examined. On the other hand, chiral sulfonimines and sulfinimines have been widely applied in asymmetric synthesis.[21] Therefore, our next

effort was to synthesize the chiral sulfonimines and to examine the possibility of the asymmetric Barbier-type allylation reaction in aqueous media.

3.4.1 Asymmetric Allylation of (S)-Camphor-10-sulfonimines

Camphor has been widely used as chiral auxiliary for asymmetric synthesis of enantiomerically pure amino acids.[22] Given the ready availability of camphor sulfonamide as the precursor, our first target was to prepare (S)-camphor-10-sulfonyl benzaldimine (**3.34**) starting from (S)-camphor-sulfonic acid **3.30** by a 4-step synthesis with 100% ee of the product **3.34**. (Scheme 3.14)



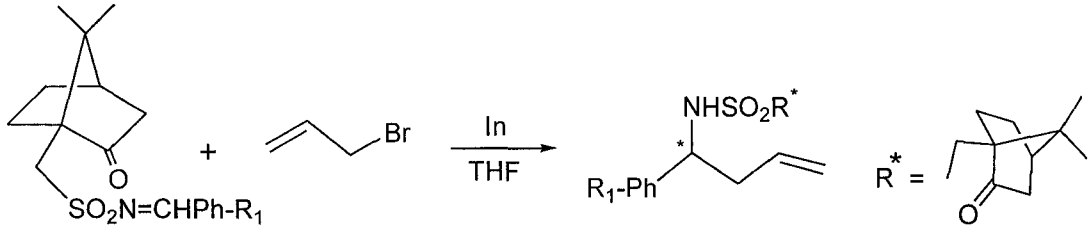
Scheme 3.14

With these (S)-camphor sulfonimines at hand, we then engaged in a careful examination of the enantioselectivity of the Barbier type allylation reaction under the following different situations.

a. Allylation Reaction of Chiral Sulfonimines in THF

To compare the different impact of organic and aqueous media on the stereochemistry of the reaction, we first investigated the reaction conducted in THF.

(Scheme 3.15) Mediated by indium, the Barbier-type allylation reaction with chiral camphorsulfonimines **3.34** can be performed smoothly in THF with high yields, however, with moderate diastereoselectivity (32% *de*). The substituents on the benzene ring did not show influence on either the yields or the selectivity (Table 3.5).



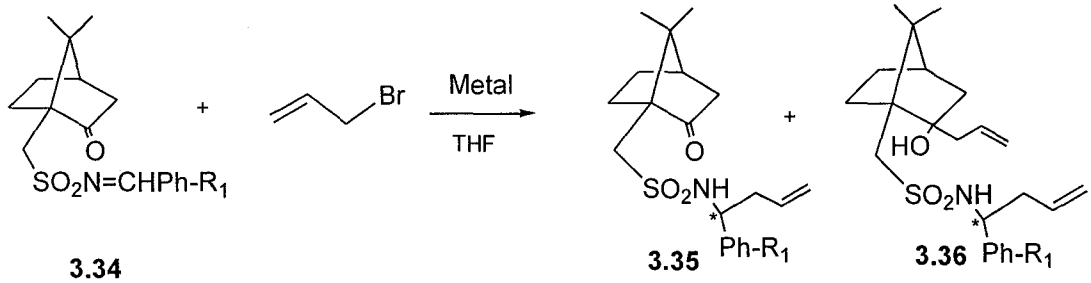
3.34 **3.35**

Scheme 3.15

Table 3.5 Barbier-type Allylation Reaction of Chiral Camphor-Sulfonimines in THF

Entry	R_1	Metal	Solvent	Yield %	de %
1	H	In	THF	90	32
2	*p*-CH_3	In	THF	92	30
3	*p*-Cl	In	THF	95	32

It is worth noting that due to the bulky environment in the camphor structure, the Barbier-type allylation reaction shows excellent chemo-selectivity on the C=N function over the C=O function in most cases. However, when an electron-donating group such as methoxyl was introduced on the benzene ring which deactivated the electrophilicity of the C=N bond, diallylation product was obtained with 37% of the final allylation products (Scheme 3.16).



3.34 **3.35** **3.36**

R_1	Metal	Ratio of 3.35 : 3.36
p-Cl	Indium	100 : 0
p-OCH_3	Indium	63 : 37

Scheme 3.16

b. Allylation Reaction of Chiral Sulfonimines in Aqueous Media

Mediated by indium:

Due to the bulky camphor group attached on the sulfonimine, the stability and reactivity of camphorsulfonimines are lower than the aromatic sulfonimines. When the reaction was conducted in aqueous media, the reaction was strongly influenced by the substituents on the substrates. When an electron-withdrawing group such as *para*-chloro group was on the benzene ring which could increase the reactivity of the C=N bond, relatively good yield could be obtained (Table 3.6, *entry 1*). However, when the (S)-camphorsulfonimines bearing electron-donating substituents, the reaction suffered from serious hydrolysis of the C=N bond in aqueous media and relatively poor yields were obtained. (Table 3.6, *entries 2,3*)

Mediated by Zinc:

When zinc powder was employed instead of indium, the Barbier-type allylation reaction could be carried out smoothly in saturated ammonium chloride aqueous solution with high yields (Table 3.6, *entries 4~7*) which are in agreement with the previous

results. The reaction showed excellent chemoselectivity without any observation of the diallyllation products even with sulfonimine **3.34d**. However, the reaction showed poor diastereoselectivity with 8~15% *de*.

Table 3.6 Barbier-type allylation reaction of chiral camphor-sulfonimines in aqueous media

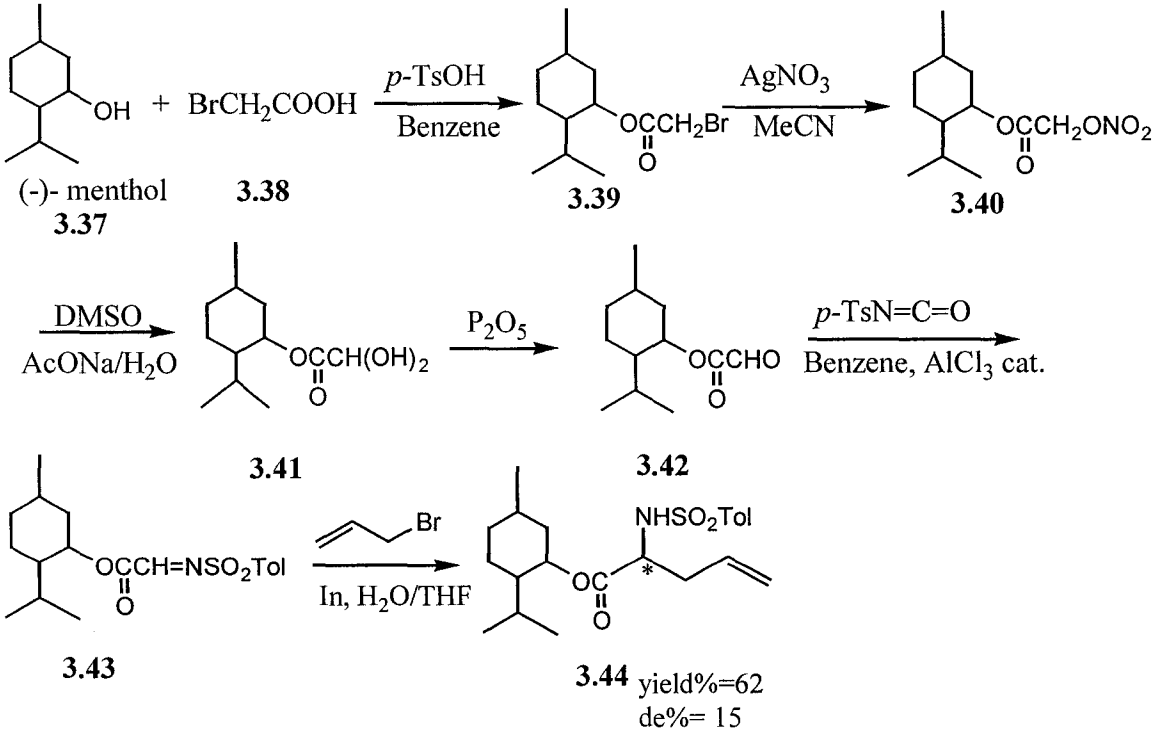
Entry	R_1	Metal	Solvent	Yield %	de %*
1	*p*-Cl	In	THF:H_2O=1:1	95	26
2	H	In	THF:H_2O=1:1	10	18
3	*p*-CH_3O	In	THF:H_2O=1:1	0	---
4	H	Zn	NH_4Cl/H_2O	92	15
5	*p*-CH_3	Zn	NH_4Cl/H_2O	92	10
6	*p*-Cl	Zn	NH_4Cl/H_2O	93	10
7	*p*-CH_3O	Zn	NH_4Cl/H_2O	90	8

**de of the products were determined by ^1H NMR of the crude products*

Apparently, the asymmetric induction from the camphor group is not as high as we anticipated. The substituents on the substrates also did not show any effect on the diastereoselectivity of the reaction. The obtained diastereoselectivities of the reaction ranged from low to moderate. The low diastereoselectivity could be due to the fact that the chiral center of the camphor group is too far away from the reacting center of the C=N bonds. Moreover, in spite of its bulkiness, camphor group is a poor chelation group for the further efficient stereocontrol in the transition state. However, it is worthy to point out that the diastereoisomers can be easily separated by flash column chromatography and each enantiopure isomer can be obtained.

3.4.2 Asymmetric Allylation of Chiral Sulfonimino-acetic Acid Ester

Aqueous allylindation of benzenesulfonylimino-acetic acid esters can provide a potential strategy to the stereoselective synthesis of α-amino acid in aqueous media. This consideration encouraged us to prepare the chiral sulfonimino-acetic acid ester **3.43** and examine its asymmetry induction in the aqueous allylation reaction. Compound **3.43** was prepared through the method in Scheme 3.17.[23] Bromo-acetic acid (-) menthyl ester **3.39** synthesized from (-)-menthol **3.37** and bromo-acetic acid **3.38**, was transferred to nitrooxy-acetic acid menthyl ester **3.40** by a nucleophilic substitution reaction with silver nitrate. The further hydrolysis of **3.40** gave dihydroxy acetal **3.41**. Menthyl glyoxylate ester **3.42** was obtained by vacuum distillation of **3.41** with P_2O_5. The reaction of tosyl isocyanate with **3.42** catalyzed by $AlCl_3$ gave the desired (-)-menthyl toluenesulfonimino-acetate **3.43** in 100% *ee*.

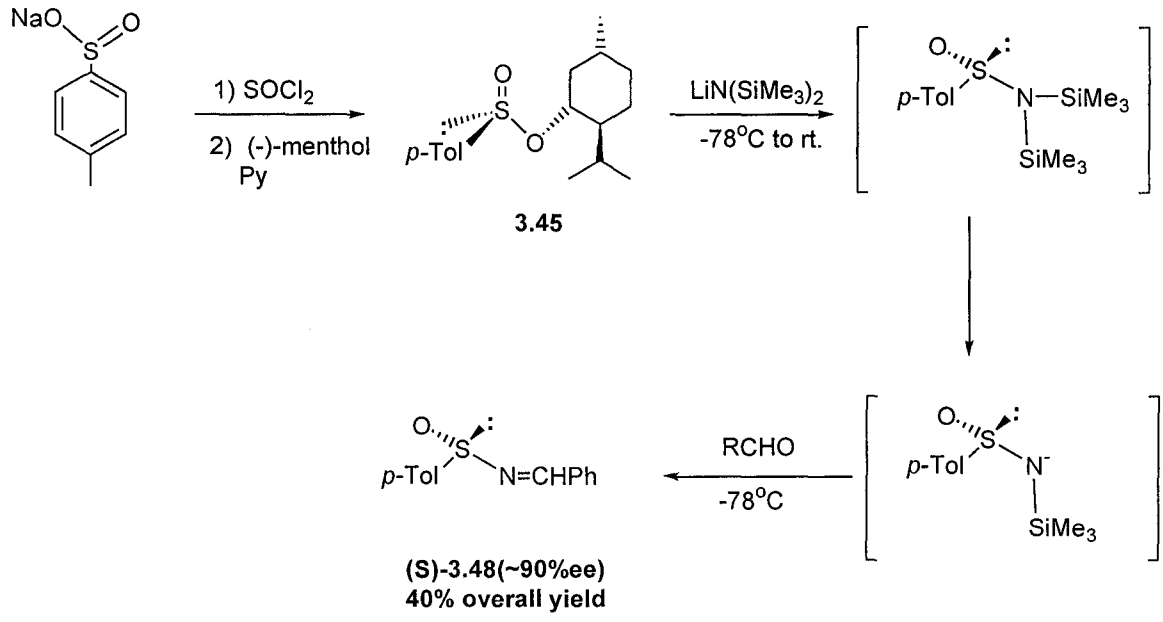


Scheme 3.17

Preliminary investigation of the aqueous allylation of **3.43** was rather disappointing. Product **3.44**, though obtained in good yield, showed only 15% *de.* The low diastereoselectivity could be attributed to the relative long distance between the menthyl stereocentre and the C=N bond reacting center. By using a modified chiral menthyl auxiliary, such as 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexanol, which can more effectively block one attacking phase, the diastereoselectivity of the reaction might be improved.

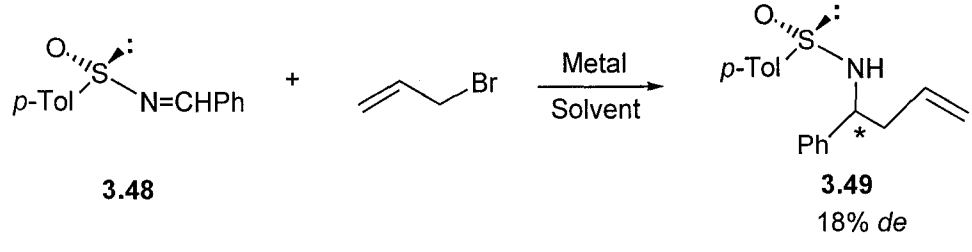
3.4.3 Asymmetric Allylation of Chiral Sulfinimine

Sulfinimines are also very good carbon nucleophile acceptors and may display unique stereoselectivity due to the existence of the chiral electron withdrawing sulfinyl group. In this case, the proximity of the chiral center on the sulphur atom to the reaction centre makes it possible to control these reactions in a better diastereoselective manner. Based on such consideration, chiral (S)-sulfinimine (**3.48**) was prepared through a 3-step synthesis with 40% of overall yield (Scheme 3.18). Sodium toluenesulfinate was firstly transformed to sulfinyl chloride, which reacted with (-)-menthol to give compound **3.45**. **3.45** was then treated with $LiN(SiMe_3)_2$ at –78 °C, followed by the addition of aldehyde to give the desired chiral sulfinimine **3.48** with 90% *ee*.



Scheme 3.18

The Barbier-type allylation of chiral sulfinimine **3.48** was then investigated (Scheme 3.19). It was found that the reaction proceeded smoothly in saturated ammonium chloride mediated by zinc powder giving the corresponding homallyllic sufinamide. However, only moderate diastereoselectivity (18% *de*) was observed. (Table 3.7)



Scheme 3.19

When mediated by indium powder, the Barbier-type allylation reaction did not proceed either in THF or in aqueous media. This may be attributed to the relatively lower electrophilicity of the sulfinimines in comparison with the corresponding sulfonimines.

The C=N bond in sulfinimines is less activated as in sulfonimines, since sulfonyl group is a stronger electron-withdrawing group than sulfinyl group.

Table 3.7 The Barbier-type allylation reactions of chiral sulfinimine

Entry	Metal	Solvent	Yield %	de %*
1	In	THF	0	----
2	In	H_2O	0	----
3	Zn	NH_4Cl/H_2O	80	18

*de was determined by ^{1}H NMR of the crude product

The low diastereoselectivity of the reaction may be attributed to the nature of the zinc mediated Barbier type reaction. The reaction is likely to go through an SET process instead of allylzinc species as intermediates. The radical mechanism decreases the possibility of chelation control in the process, and hence, lowers the diastereoselectivity of the reaction.[24]

3.5 Conclusion

In our effort to have a better understanding of the stereo factors in the indium-mediated Barbier type allylation of sulfonimines, the diastereoselectivity of the reaction was carefully studied by using γ-substituted allylic bromides, In the cinnamylation of benzenesulfonimine **3.1**, the reaction gave only *syn* isomer **3.3b**. The diastereoselectivity of the crotylation reaction seemed to be solvent dependant. When a proximal chelation function such as 2-hydroxyl function on the benzene ring of benzenesulfonimine, similar

syn-selectivity was obtained regardless of the reaction media. The diastereoselectivity can be further improved by introducing a α-chelating function. Three cases of chiral sulfonimines or sulfinimine were examined as the substrates for the aqueous asymmetric allylation reaction. Only moderate stereoselectivity was found.

3.6 Experimental Section

General Aspect: see Chapter 2, Experimental Section.

3.6.1 Typical procedure of the synthesis of sulfonimines with proximal chelating function.

a. N-(1H-Pyrrol-2-ylmethylene)-benzenesulfonamide (3.18d):

A solution of 1H-pyrrole-2-carbaldehyde (10 mmol) in dichloromethane (50 mL) was cooled to 0 °C under argon and was treated with triethylamine (30 mmol, 3eq.) and benzenesulfonamide (10 mmol, 1eq.). Titanium Tetrachloride (1.1 eq.) was added dropwise to the reaction solution. The reaction was monitored by TLC and lasted over night, then was quenched by adding iced water (20 mL). The aqueous phase was extracted by methylene chloride (3 × 20 mL), and the combined organic layer was washed with brine and dried over sodium sulfate. Sulfonimines were obtained by evaporate the solvent and further purified via recrystallization (dichloromethane and hexane) in 35% yield. yellow crystal. ^{1}H NMR (200 MHz, $CDCl_3$) 9.5 (br, 1H), 8.75 (s, 1H), 7.98-7.90 (m, 2H), 7.65-7.46 (m, 3H), 7.20-7.17 (m, 1H), 7.08-7.02 (m, 1H), 6.45-6.38 (m, 1H)

N-(2-Hydroxy-benzylidene)-benzenesulfonamide (3.15a) yellow solid, mp 110-112 °C. ^{1}H NMR (200 MHz, $CDCl_3$) 10.80 (s, 1H), 9.14 (s, 1H), 8.04-7.96 (m, 2H), 7.70-7.50 (m, 5H), 7.02-6.98 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 171.62, 144.20, 137.70, 135.69, 134.13, 129.67, 128.18, 120.74, 118.41, 117.04, 112.80

N-(2-Methoxy-benzylidene)-benzenesulfonamide (3.15b) white solid, mp 64-66 °C. ^{1}H NMR (200 MHz, $CDCl_3$) 9.58 (s, 1H), 8.10-7.98 (m, 3H), 7.64-7.48 (m, 4H), 7.02-6.92 (m, 2H), 3.92 (s, 3H)

N-(4-Hydroxy-benzylidene)-benzenesulfonamide (3.15e) white solid, 89-93 °C decompose. ^{1}H NMR (200 MHz, $CDCl_3$) 9.90 (br., 1H), 8.90 (s, 1H), 8.02-7.99 (m, 2H), 7.82-7.78 (m, 2H), 7.62-7.48 (m, 3H), 6.98-6.90 (m, 2H).

b. N-Furan-3-ylmethylene-*p*-toluenesulfonamide (3.18b)

A suspension of tellium (0.7 g, 5.5 mmol, 0.55 eq.) and chloramine-T (2.4 g, 10 mmol, 1 eq.) in toluene (20 mL) was stirred and refluxed for 1hr. Then 3-furaldehyde (0.87 mL, 10 mmol, 1eq.) was added dropwise via syringe. The mixture was continue refluxing 2hr. The reaction mixture was filtered through Celite by adding methylene chloride. N-Furan-3-ylmethylene-*p*-toluenesulfonamide was obtained as white crystal by concentration and recrystllization via methylene chloride and hexane. ^{1}H NMR (400 MHz, $CDCl_3$) 8.99 (s, 1H), 8.08-8.06 (m, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.52-7.48 (m, 1H), 7.33 (d, J = 8.4 Hz, 2H), 6.85-6.83 (m, 1H), 2.43 (s, 3H).

3.6.2 Synthesis of Sulfonimino Acetic Acid Ester.

a. **Preparation of isopropyl glyoxylate (3.22)**

To a solution of diisopropyl tartrate (10 mmol) in dichloromethane (30 mL) and saturated sodium bicarbonate solution (2 mL) was treated with sodium periodate (20 mmol, 2eq.). The mixture was stirred over night and monitored by TLC. The reaction mixture was filtered through Celite and dried over sodium sulfate. Pure isopropyl glyoxylate **3.22** was obtained by vacuum distillation (40 °C/10 mmHg) of the crude product together with phosphorous pentaoxide (0.5 g). The obtained glyoxylate **3.22** must be used immediately. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.39 (s, 1H), 5.3-5.2 (q, 1H, J = 6.12 Hz), 1.35 (d, 6H, J = 6.12 Hz)

b. **N-Tosyl imino-2-acetic acid, isopropyl ester** [25] **(3.23b)**

To the solution of anhydrous and freshly distilled glyoxylic acid isopropyl ester (5 mmol) in dry benzene (20 mL), were added *p*-toluene-sulfonylisocyanate (5.5 mmol, 1.1 eq.) and catalytic amount of aluminum chloride (5% mol). The solution thus obtained was refluxed for 4 hrs and the solvent was removed by distillation under vacuum until viscous oil was obtained as the expected product. This oil must be used immediately or stored in refrigerator below 0 °C for usage within one week. ^{1}H NMR (200 MHz, $CDCl_3$) 8.24 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 5.28-5.15 (q, J = 6.2 1H), 2.47 (s, 3H), 1.33 (d, J = 6.2 Hz, 6H).

3.6.3. Typical procedure of crotylation of sulfonimines

To a rigorously stirred mixture of crotyl bromide (1.5mmol, 3eq.) and sulfonimine (0.5 mmol, 1eq.) in solvent (4mL), was added indium powder (1.5mmol, 3eq.) in one portion. The reaction was stirred for 6 hrs and quenched by adding 1N HCl (2 mL). The aqueous layer was extracted by diethyl ether (3 × 20 mL). The combined organic phase was

washed with saturated sodium bicarbonate and brine respectively, and dried over sodium sulfate. After evaporation of solvent, the pure allylation product was obtained via silica gel flash column chromatography with 10% ethyl acetate in hexane as eluent.

N-[1-(2-Hydroxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide (3.16a) white solid, mp 98-100 °C; major *syn isomer*: ^{1}H NMR (200 MHz, $CDCl_3$): ppm 7.70-7.58 (m, 2H), 7.40-7.25 (m, 3H), 6.95-6.85 (m, 1H), 6.72-6.50 (m, 3H), 6.20 (br., 1H), 5.89 (d, 1H, J =9.6 Hz), 5.51-5.37 (m, 1H), 4.91-4.80 (m, 2H), 4.20-4.11 (m, 1H), 2.81-2.61 (m, 1H), 1.13 (d, 3H, J =6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): ppm 152.89, 140.21, 139.97, 132.52, 130.09, 128.84, 127.10, 125.06, 120.30, 116.53, 116.25, 62.73, 43.82, 18.49; *anti* isomer: ^{1}H NMR (200 MHz, $CDCl_3$): ppm 7.70-7.58 (m, 2H), 7.40-7.25 (m, 3H), 6.95-6.85 (m, 1H), 6.72-6.50 (m, 3H), 6.20 (br., 1H), 5.60 (d, 1H, J =9.0 Hz), 5.80-5.67 (m, 1H), 5.17-5.09 (m, 2H), 4.19-4.11 (m, 1H), 2.81-2.61 (m, 1H), 0.81 (d, 3H, J =6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 153.18, 140.66, 139.84, 132.80, 129.92, 128.69, 127.21, 125.01, 120.52, 116.74, 115.79, 62.19, 43.64, 19.12; IR (neat on NaCl, cm^{-1}): 3421.7, 3314.2, 1609.3, 1457.0, 1311.8, 1157.8; MS (FAB) 318 (M+1, 31.7), 154 (100); HRMS (FAB), calcd. for $C_{17}H_{19}NO_3S+H^+$ 318.11626, found 318.11639; Anal. Calcd. for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; found C, 64.36; H, 6.39; N, 4.34.

N-[1-(2-Methoxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide (3.16b) colorless solid, mp 93-95 °C; *syn* isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.55-7.47 (m, 2H), 7.34-7.26 (m, 1H), 7.21-7.10 (m, 2H), 7.01-6.95 (m, 1H), 6.70-6.52 (m, 3H), 5.57 (d, 1H, J = 10.4 Hz), 5.48-5.31 (m, 1H), 4.85-4.75 (m, 2H), 4.27-4.18 (m, 1H), 3.69 (s, 3H),

2.80-2.51 (m, 1H), 1.10 (d, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 156.13, 140.31, 132.07, 130.08, 128.70, 128.63, 128.54, 127.06, 126.90, 120.55, 115.51, 110.98, 62.40, 56.23, 43.98, 18.59; *anti* isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.21-7.10 (m, 2H), 7.01-6.95 (m, 1H), 6.70-6.52 (m, 3H), 5.83-5.90 (m, 1H), 5.39 (d, 1H, J = 10.2 Hz), 5.08-4.98 (m, 2H), 4.27-4.18 (m, 1H), 3.69 (s, 3H), 2.80-2.51 (m, 1H), 0.79 (d, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 140.64, 140.56, 132.07, 129.78, 128.76, 128.63, 128.54, 127.06, 126.90, 120.66, 116.22, 110.98, 61.68, 56.23, 43.65, 19.04; IR (neat on NaCl, cm^{-1}): 3288.2, 2965.8, 1601.6, 1447.3, 1324.7, 1163.5; MS (FAB), 332 (M+1, 45), 175 (100); HRMS (FAB), calcd. for $C_{18}H_{21}NO_3S+H^+$ 332.13204, found 332.13216; Anal. Calcd. for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; found C, 65.14; H, 6.77; N, 4.18.

N-[1-(3-Hydroxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide (3.16c) white solid; mp 94-98 °C major *syn isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): 7.65-7.57 (m, 2H), 7.47-7.37 (m, 1H), 7.35-7.24 (m, 2H), 7.03-6.91 (m, 1H), 6.61-6.44 (m, 3H), 5.44-5.35 (m, 1H), 5.04-4.95 (m, 2H), 5.23 (br. 1H), 4.22 (dd, 1H, J = 8.4, 5.8 Hz), 2.58-2.40 (m, 1H), 0.91 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 155.59, 141.2, 140.24, 138.86, 132.59, 129.42, 128.85, 127.22, 120.07, 117.18, 114.55, 114.53, 61.72, 43.90, 16.34; *anti isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): 7.65-7.57 (m, 2H), 7.47-7.37 (m, 1H), 7.35-7.24 (m, 2H), 7.03-6.91 (m, 1H), 6.61-6.44 (m, 3H), 5.56-5.46 (m, 1H), 5.14-5.08 (m, 2H), 5.19 (br. 1H), 4.02 (dd, 1H, J = 8, 6.1 Hz), 2.42-2.29 (m, 1H), 0.81 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 155.59, 141.55, 139.46, 132.56, 129.59, 128.78, 127.30, 120.07, 117.81, 114.71, 114.41, 62.15, 44.63, 17.20; IR (neat on NaCl, cm^{-1}):

2821.1, 1457.1, 1318.3, 1155.7; MS (FAB): 356 ($M+K^+$, 12), 307 (100); HRMS (FAB), calcd. for $C_{17}H_{19}NO_3S+K^+$ 356.0723, found. 356.0724; Anal. Calcd. for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; found C, 64.61; H, 6.47; N, 4.40.

N-[1-(3-Methoxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide (3.16d) white solid, mp 88-90 °C; s*yn isomer*: ^{1}H NMR (300 MHz, $CDCl_3$): ppm 7.62-7.54 (m, 2H), 7.43-7.38 (m, 1H), 7.30-7.26 (m, 2H), 7.08-7.01 (m, 1H), 6.67-6.63 (m, 2H), 6.55-6.50 (m, 1H), 5.50-5.40 (m, 1H), 5.07-5.02 (m, 1H), 4.91 (d, 1H, J = 8.4 Hz), 4.30-4.26 (dd, 1H, J = 7.8, 6.3 Hz), 3.67 (s, 1H), 2.58-2.49 (m, 1H), 0.93 (d, 3H, 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 159.91, 139.52, 132.31, 129.39, 128.83, 128.72, 127.37, 127.29, 120.36, 118.07, 113.42, 113.24, 63.16, 56.25, 45.80, 18.66; *anti isomer*: ^{1}H NMR (200 MHz, $CDCl_3$): 7.62-7.54 (m, 2H), 7.43-7.38 (m, 1H), 7.30-7.26 (m, 2H), 7.08-7.01 (m, 1H), 6.67-6.63 (m, 2H), 6.55-6.50 (m, 1H), 5.66-5.53 (m, 1H), 5.18-5.12 (m, 1H), 4.86 (d, 1H, J = 8.2 Hz), 4.10-4.05 (dd, 1H, J = 8.1, 5.4 Hz), 3.67 (s, 1H), 2.44-2.37 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 159.91, 140.86, 138.85, 129.25, 128.83, 128.72, 128.38, 127.29, 120.28, 117.38, 113.67, 113.09, 62.72, 56.25, 45.04, 17.88; IR (neat on NaCl, cm^{-1}): 3285.7, 2966.6, 1601.8, 1448.4, 1321.3, 1161.0; MS (CI) 332 (M+1, 1.8), 276 (100); HRMS (FAB), calcd. for $C_{18}H_{21}NO_3S+H^+$ 332.13204, found. 332.13193; Anal. Calcd. for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; found C, 65.23; H, 6.61; N, 4.21.

N-[1-(4-Hydroxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide (3.16e), white solid; mp 100-104 °C major *syn isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): 7.62-7.52(m, 2H),

7.46-7.38 (m, 1H), 7.36-7.26 (m, 2H), 6.88 (d, 2H, J = 8.4 Hz) 6.55 (d, 2H, J = 8.4 Hz), 5.52-5.34 (m, 1H), 4.99-4.86 (m, 2H), 4.96 (br., 1H), 4.23 (dd, 1H, J = 8, 5.2 Hz), 2.54-2.44 (m, 1H), 0.90 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 154.90, 138.85, 133.08, 128.94, 128.86, 127.21, 126.67, 117.33, 114.99, 61.30, 44.09, 16.59; *anti isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): 7.62-7.52(m, 2H), 7.46-7.38 (m, 1H), 7.36-7.26 (m, 2H), 6.88 (d, 2H, J = 8.4 Hz) 6.55 (d, 2H, J = 8.4 Hz), 5.66-5.56 (m, 1H), 5.18-5.08 (m, 2H), 4.87 (br., 1H), 4.00 (dd, 1H, J = 8, 4.6 Hz), 2.44-2.28 (m, 1H), 0.79 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):154.90, 140.69, 132.37, 130.57, 129.42, 128.74, 127.32, 126.67, 117.33, 115.17, 61.80, 45.03, 17.27; IR (neat on NaCl, cm^{-1}): 2850.4, 1515.7, 1447.1, 1310.9, 1156.7; MS (FAB): 356 ($M+K^+$, 13), 161 (100); HRMS (FAB), calcd. for $C_{17}H_{19}NO_3S+K^+$ 356.0723, found. 356.0724; Anal. Calcd. for $C_{17}H_{19}NO_3S$ C, 64.33; H, 6.03; N, 4.41; found C, 64.12, H, 6.45; N, 4.36.

N-(1-Furan-2-yl-2-methyl-but-3-enyl)-benzenesulfonamide (3.19a) white solid, mp 105-106 °C; *syn* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): ppm 7.69-7.64 (m, 2H), 7.48-7.41 (m, 1H), 7.38-7.31 (m, 2H), 7.01-7.06 (m, 1H), 6.05-6.02 (m, 1H), 5.83 (d, 1H, J = 3 Hz), 5.60-5.46 (ddd, 1H, J = 16.8, 10.2, 8.7Hz), 5.12-5.04 (m, 2H), 5.05(br., 1H), 4.35 (dd, 1H, J = 9.6, 5.7 Hz), 2.70-2.52 (m, 1H), 0.97 (d, 3H, J = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): ppm 151.17, 141.90, 140.70, 138.69, 132.43, 128.97, 127.24, 127.16, 117.53, 110.35, 108.58, 56.71, 44.38, 18.34; IR (neat on NaCl, cm^{-1}), 3251.6, 1449.0, 1321.8, 1163.8, 910.3, 731.7; MS (FAB) 292 (M+1, 25.4), 236 (73.2), 135 (100); HRMS calcd. for $C_{15}H_{17}NO_3S+H^+$ 292.10074, found 292.10064; Anal. Calcd. for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; found C, 62.23;H, 6.10; N, 4.82.

N-(1-Furan-3-yl-2-methyl-but-3-enyl)-4-methyl-benzenesulfonamide (3.19b) white solid; mp 91-94 °C syn isomer: ^{1}H NMR (400 MHz, $CDCl_3$): ppm 7.61 (d, 2H, *J*=8.8 Hz), 7.17 (d, 2H, *J*= 8.8 Hz), 7.16 (m, 1H), 7.00 (d, 1H, *J*=0.8 Hz), 6.04 (d, 1H, *J*=1.6 Hz), 5.57-5.48 (m, 1H), 5.15 (d, 1H, *J*=8.8 Hz), 5.05-5.01 (m, 2H), 4.25 (dd, 1H, *J*=8.8, 5.6 Hz), 2.51-2.42 (m, 1H), 2.37 (s, 3H), 0.94 (d, 3H, *J*=6.4 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): ppm 143.38, 143.08, 140.23, 138.91, 137.93, 129.54, 127.34, 123.31, 117.29, 109.4154.19, 43.32, 21.72, 16.57; IR (neat on NaCl, cm^{-1}): 2965.4, 1499.6, 1329.0, 1162.4, 1025.9; MS (EI), 306 (M+1, 0.4), 250 (100); Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; found C, 63.01; H, 6.64; N, 4.62.

N-(1-Furan-2-yl-2-methyl-but-3-enyl)-4-methyl-benzenesulfonamide (3.19c) colorless crystal; mp 94-95 °C *syn* isomer: ^{1}H NMR (400 MHz, $CDCl_3$): ppm 7.55 (d, 2H, *J*=8 Hz), 7.15 (d, 2H *J*=8 Hz), 7.11 (m, 1H), 6.08-6.07 (m, 1H), 5.85 (d, 1H, *J*=3.2 Hz), 5.48-5.49 (m, 1H), 5.07-5.02 (m, 2H), 4.87 (d, 1H, *J*=9.6 Hz), 2.62-2.54 (m, 1H), 2.36 (s, 3H), 0.97 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): ppm 151.50, 143.18, 141.97, 138.77, 137.78, 129.52, 127.12, 117.39, 110.04, 108.26, 55.66, 43.31, 21.71, 16.98; IR (neat on NaCl, cm^{-1}): 1422.4, 1320.1, 1159.9, 1009.3; MS (FAB): 344 ($M+K^+$, 14), 135 (100); HRMS (FAB), calcd. for $C_{16}H_{19}NO_3S+K^+$ 344.0723, found. 344.0722; Anal. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; found, C, 62.99; H, 6.30; N, 4.59.

N-[2-Methyl-1-(1H-pyrrol-2-yl)-but-3-enyl]-benzenesulfonamide (3.19d), yellow solid; decompose at 103-105 °C; major *syn* isomer: ^{1}H NMR (200 MHz, $CDCl_3$): 8.35 (br. 1H), 7.76 (d, 2H), 7.55 (t, 1H), 7.45 (t, 2H), 6.60 (m, 1H), 6.02 (m, 1H), 5.87 (s, 1H),

5.52 (ddd, 1H, J = 10.50, 10.00, 7.00 Hz), 5.04-4.96 (m, 2H), 4.81 (d, 1H, J = 7.00 Hz), 4.34 (dd, 1H, J = 8.5, 5.5 Hz), 2.64-2.60 (m, 1H), 0.96 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 140.24, 139.32, 132.87, 129.17, 127.35, 117.89, 116.95, 108.34, 107.13, 55.91, 42.07, 16.00; IR (neat on NaCl, cm^{-1}): 2950, 1447.8, 1310, 1158.7; MS(FAB) 291 (M+1, 10), 235 (100); HRMS (FAB), calcd. for $C_{15}H_{18}N_2O_2S+H^+$ 291.1167, found. 291.1168.

N-(2-Methyl-1-thiophen-2-yl-but-3-enyl)-benzenesulfonamide (3.19e), clear oil, major *syn* isomer: ^{1}H NMR (200 MHz, $CDCl_3$): 7.65-7.60 (m, 2H), 7.45-7.20 (m, 3H), 7.04 (dd, 1H, J = 5.0, 1.4 Hz), 6.72 (dd, 1H, J = 5.2, 3.6 Hz), 6.61-6.58 (m, 1H), 5.61 (ddd, 1H, J = 10.2, 9.8, 8.0 Hz), 5.13-5.04 (m, 2H), 4.95 (d, 1H, J = 8.6 Hz), 4.62 (dd, 1H, J = 8.8, 6.0 Hz), 2.59 (m, 1H), 0.99 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 141.70, 140.37, 138.07, 132.10, 128.50, 126.78, 126.08, 125.74, 124.52, 117.37, 57.56, 44.03, 16.35; IR (neat on NaCl, cm^{-1}): 2935.8, 1448.8, 1320.8, 1160.9; MS(FAB) 346 ($M+K^+$, 10), 151(100); HRMS (FAB), calcd. for $C_{15}H_{17}NO_2S_2+K^+$ 346.0338, found. 346.0337; Anal. Calcd. for $C_{15}H_{17}NO_2S_2$: C, 58.60; H, 5.57; N, 4.56; found C, 58.71; H, 5.63; N, 4.55.

3-Methyl-2-(toluene-4-sulfonylamino)-hex-5-enoic acid, butyl ester (3.34a) white solid mp 52-53 °C; major *syn* isomer: ^{1}H NMR (200 MHz, $CDCl_3$): 7.69 (d, 2H, J = 8.34 Hz), 7.26 (d, 2H, J = 8.34 Hz), 5.73-5.55 (m, 1H), 5.13-5.01 (m, 2H), 5.07 (br, 1H), 3.84-3.75 (m, 1H), 3.86-3.76 (m, 2H), 2.60-2.40 (m, 1H), 2.40 (s, 3H), 1.49-1.32 (m, 2H), 1.33-1.15 (m, 2H), 1.03 (d, 3H, J = 6.96 Hz), 0.88 (t, 3H, J = 7.26 Hz); ^{13}C NMR (50

MHz, $CDCl_3$): 170.47, 143.66, 138.20, 136.98, 129.82, 127.65, 117.16, 66.29, 61.03, 43.04, 31.78, 23.07, 20.56, 17.48, 15.23; IR (neat on NaCl, cm^{-1}): 3277.4, 2962.6, 1737.2, 1598.6, 1343.9, 1163.7; MS(FAB) 340 (M+1, 2.5), 283 (100), 154 (100); HRMS (FAB), calcd. for $C_{17}H_{25}NO_4S+H^+$ 340.1582, found. 340.1582; Anal. Calcd. for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13; found C, 60.49; H, 7.77; N, 4.18.

3-Methyl-2-(toluene-4-sulfonylamino)-hex-5-enoic acid, isopropyl ester (3.34b) white solid ; mp 92-95 °C; major *syn* isomer: ^1H NMR (200 MHz, $CDCl_3$): 7.69 (d, 2H, J = 8.16 Hz), 7.25 (d, 2H, J = 8.10 Hz), 6.65 (ddd, 1H, J = 10.14, 10.10, 8.10 Hz), 5.19 (d, 1H, J = 10.26 Hz), 5.09-5.01 (m, 2H), 4.69 (dt, 1H, J = 12.58, 6.22 Hz), 3.76 (dd, 1H, J = 10.14, 5.70 Hz), 2.48 (d, 1H, J = 6.88 Hz), 2.39 (s, 3H), 1.13-0.94 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): 169.90, 143.68, 138.29, 137.01m 129.85, 127.65, 117.08, 70.44, 60.96, 43.12, 23.09, 22.99, 17.49; IR (neat on NaCl, cm^{-1}): 1720.9, 1334.2, 1163.5, 1087.7; MS(CI), 326 (M+1, 100), 238 (96); HRMS (FAB), calcd. for $C_{16}H_{23}NO_4S+H^+$ 326.1426, found. 326.1426, Anal. Calcd. for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30; found C, 59.16; H, 7.29; N, 4.32.

3.6.4 Configuration confirmation

a. **[2-(1-Benzenesulfonylamino-but-3-enyl)-phenyl]-phosphonic acid diethyl ester (3.12)**

To a solution of N-[1-(2-hydroxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide **3.16a** (1 mmol) in triethylamine (5 mL) in an ice bath, was added diethyl chlorophosphate (1.2mmol, 1.2 eq.) dropwise. The mixture was heated at 60 °C over

night. The reaction was quenched by adding saturated NH_4Cl (10 mL) and extracted with diethyl ether (2 X 15 mL). After evaporation of the solvent, the product was obtained as clear oil through silica gel flash column chromatography with 20% ethyl acetate in hexane as eluent. Colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$): major isomer: 7.66-7.58 (m, 2H), 7.38-7.16 (m, 4H), 7.10-6.98 (m, 1H), 6.90-6.74 (m, 2H), 5.84 (d, 1H, J = 9.08 Hz), 5.50-5.34 (m, 1H), 4.93-4.80 (m, 2H), 4.31-4.13 (m, 4H), 2.74-2.52 (m, 1H), 1.35 (dt, 6H, J = 7.04, 1.38 Hz), 1.02 (d, 3H, J = 6.78 Hz); minor isomer 7.66-7.58 (m, 2H), 7.38-7.16 (m, 4H), 7.10-6.98 (m, 1H), 6.90-6.74 (m, 2H), 5.84 (d, 1H, J = 9.08 Hz), 5.68-5.52 (m, 1H), 5.10-4.95 (m, 2H), 4.52-4.36 (m, 4H), 2.74-2.52 (m, 1H), 1.35 (dt, 6H, J = 7.04, 1.38 Hz), 0.85 (d, 3H, J = 6.76 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): major isomer: 140.15, 139.64, 138.61, 128.94, 128.86, 127.82, 126.22, 123.67, 118.73, 115.38, 65.08, 65.02, 42.82, 16.87, 16.74; minor isomer: 147.02, 139.54, 131.32, 129.08, 128.28, 127.75, 126.22, 123.78, 118.73, 116.54, 65.15, 64.94, 42.89, 17.60, 16.64

b. **General method for reduction of aryl diethyl phosphate ester.** [26]

Anhydrous titanium (IV) tetrachloride (3 mmol, 3eq.) was stirred in dry toluene (10 mL) and potassium metal (cut in small pieces, 12 mmol, 12 eq.) was added under argon. This slurry was then stirred at reflux for 1 hr until no trace of potassium metal was visible. The diethyl aryl phosphate ester **3.12** (1 mmol, 1eq.) was added and the mixture was stirred at reflux for 8 hr. The reaction mixture was then cooled in an ice bath and quenched with methanol (2 mL) and filtered through Celite/silica gel (4:1 w/w). The filtrate was concentrated in vacuo to give the corresponding aryl sulfonamide sufficiently pure for NMR characterization. ^{1}H NMR (500 MHz, $CDCl_3$) *syn* isomer 7.60-7.58 (m, 1H), 7.42-

7.36 (m, 1H), 7.28-7.24 (m, 3H), 7.13-7.08 (m, 3H), 6.93-6.89(m, 2H), 5.48-5.41 (m, 1H), 5.40-5.05 (m, 2H), 4.95 (d, 1H, J = 8.0 Hz), 4.30 (m, 1H), 2.58-2.50 (m, 1H), 0.93 (d, 3H, J = 7.0 Hz); anti isomer 7.55-7.52 (m, 1H), 7.40-7.36 (m, 1H), 7.28-7.24 (m, 3H), 7.13-7.08 (m, 3H), 7.03-6.99 (m, 2H), 5.62-5.54 (m, 1H), 5.18-5.12 (m, 2H), 4.98 (d, 1H, J = 8.0 Hz), 4.10 (m, 1H), 2.44-2.38 (m, 1H), 0.83 (d, 3H, J = 7.0 Hz). The ratio of *syn : anti* is 76:24.

c. **Preparation of methylation product 3.13.** [27]

N-[1-(2-Hydroxy-phenyl)-2-methyl-but-3-enyl]-benzenesulfonamide **3.16a** (0.2 mmol) was stirred with potassium carbonate in dried acetone till the solution became a white suspension. Methyl iodide (0.42 mmol, 2.1 eq.) was added dropwise and the reaction mixture was stirred over night. The reaction mixture was filtered through Celite and washed with diethyl ether (30 mL). The filtrate after evaporation gave the methylation product **3.13**, which was pure enough for proton NMR characterization. ^{1}H NMR (400 MHz, $CDCl_3$) *syn* isomer 7.54-7.45 (m, 2H), 7.42-7.10 (m, 5H), 6.90-6.80 (m, 1H), 6.74-6.62 (m, 1H), 5.60-5.40 (m, 1H), 5.32-5.21 (m, 2H), 3.59 (s, 3H), 2.83 (s, 3H), 1.27 (d, J = 6.68 Hz, 3H); *anti* isomer 7.54-7.45 (m, 2H), 7.42-7.10 (m, 5H), 6.90-6.80 (m, 1H), 6.74-6.62 (m, 1H), 6.06-5.88 (m, 1H), 4.98-4.76 (m, 2H), 3.61 (s, 3H), 2.81 (s, 3H), 0.81 (d, J = 6.58 Hz, 3H).

3.6.5 Synthesis of 10-(S)-Camphorsulfonimine (3.34)

a. (S)-Camphor sulfonyl chloride (3.31)[28]

In a 50 mL round bottom flask cooled in ice bath, (S)-camphorsulfonic acid (5.8 g, 25 mmol) and $SOCl_2$ (11.9 g, 100 mmol) were mixed together. The reaction mixture was stirred for 4 hr and then was poured onto crushed ice (200 g). (S)-camphorsulfonyl chloride **3.31** was collected on a suction filter and washed with cold water.

b. (S)-Camphor sulfonamide 3.32

The obtained (S)-camphorsulfonyl chloride was dissolved in methylene chloride (50 mL). NH_4OH (60 mL, reagent grade) was added to the solution via a dripping funnel under vigorous stirring. The reaction was left over night and transferred to a separation funnel and the phases were separated. The aqueous phase was washed by methylene chloride (2 X 15 mL). Combined organic phase was dried over Na_2SO_4. (S)-Camphorsulfonamide **3.32** was obtained by evaporation of organic solvent, and was purified via recrystallization (methylene chloride, hexane). mp 125-128°C, white solid.

c. Preparation of (S)-Camphorsulfonimine (3.34)

(S)-camphorsulfonamide (2.31 g, 10 mmol) and diethoxymethylbenzene (1.80g, 10 mmol) were mixed together in a 10 mL round bottom flask and heated up to 150 °C until there was no ethanol released. Then the mixture was put under vacuum to cool down to give crude product. Pure sulfonimine **3.34** (except **3.34d** as colorless oil) was obtained by recrystallization (methylene chloride and hexane).

(1'S)-N-Camphor-19-sulfonyl benzaldimine (3.34a). white solid, mp 112-114 °C, ^1H NMR (200 MHz, $CDCl_3$): δ 9.1(s, 1H), 8.0 (d, J = 10.4 Hz, 2H), 7.5-7.7 (m, 3H), 3.7 (d, J = 15.6 Hz, 1H), 3.1 (d, J = 15.6 Hz, 1H), 2.4 (m, 1H), 1.8-2.2 (m, 4H), 1.4 (m, 1H), 1.2 (s, 3H), 0.9 (s, 3H), $[\alpha]^{20}_D$ 21.3 (c, 1.35, CH_2Cl_2), [lit.[29] $[\alpha]^{20}_D$ 20.6(c, 1, CH_2Cl_2)]

(1'S)-N-Camphor-19-sulfonyl tolualdimine (3.34b). white solid, mp 78-80 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.0(s, 1H), 7.9 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 3.7 (d, J = 15 Hz, 1H), 3.1 (d, J = 15 Hz, 1H), 2.8 (m, 1H), 2.5 (s, 3H), 2.35 (m, 1H), 1.7-2.2 (m, 4H), 1.4 (m, 1H), 1.2 (s, 3H), 0.95 (s, 3H).

(1'S)-N-Camphor-19-sulfonyl anisaldimine (3.34d) colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.9(s, 1H), 7.9 and 7.0 (d, J = 10.4 Hz, 2H), 3.85 (s, 3H), 3.6 (d, J = 15.6 Hz, 1H), 3.1 (d, J = 15.6 Hz, 1H), 2.6 (m, 1H), 2.35 (m, 1H), 1.65-2.2 (m, 4H), 1.4 (m, 1H), 1.2 (s, 3H), 0.85 (s, 3H).

C-(7,7-Dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-(1-phenyl-but-3-enyl)-methanesulfonamide (3.35a) For experimental procedure, see section **3.6.3.** clear oil, isomer 1 (minor) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 6.20 (d, J = 7 Hz, 1H), 5.74-5.64 (m, 1H), 5.16-5.08 (m, 2H), 4.61-4.55 (m, 1H), 2.68-2.62 (m, 1H), 2.60-2.50 (m, 3H), 2.35-2.28 (m, 1H), 2.18-1.82 (m, 5H), 1.42-1.38 (m, 1H), 0.77 (s, 3H), 0.42(s, 3H); ^{13}C NMR(50 MHz, $CDCl_3$): δ 215.96, 140.91, 133.96, 129.10, 128.20, 127.88, 118.69, 60.61, 60.07, 53.34, 49.77, 44.10, 43.91, 42.94, 28.97, 21.40, 20.81; isomer 2 (major), clear oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.22 (m, 5H), 5.72-5.64 (m, 1H), 5.56 (d, J = 7.0 Hz, 1H),5.18-5.10 (m, 2H), 4.64-4.60 (m, 1H), 3.27 (d, J = 16.5 Hz, 1H), 2.80 (d, J = 16.5 Hz, 1H), 2.62-2.58 (2H, m), 2.40-2.36 (1H, m), 2.22-1.72 (m, 5H), 1.42-1.38 (m, 1H), 0.99 (s, 3H), 0.85 (s, 3H); ^{13}C NMR(125 MHz, $CDCl_3$): δ 215.84, 141.24, 133.26, 128.50, 127.49, 126.58, 118.95, 58.89, 57.39, 51.43, 48.17, 42.67, 42.65, 41.73, 26.74, 26.19, 19.71, 19.42

C-(7,7-Dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-(1-p-tolyl-but-3-enyl)-methanesulfonamide (3.35b), clear oil, major isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-7.2(m, 4H), 5.80--5.55 (m, 1H), 5.22 (d, J = 6.8 Hz, 1H), 5.20-5.10 (m, 2H), 4.60-4.55 (m, 1H), 3.22 and 2.75 (d, J = 18.5 Hz, 1H), 2.70-2.50 (m, 2H), 2.35, (s, 3H), 2.45-1.70 (m, 6 H), 1.50-1.30 (m, 1H), 1.10, 0.85 (s, 3H), minor isomer: 7.4-7.2(m, 4H), 6.22 (d, J = 7.4 Hz, 1H), 5.80-5.55 (m, 1H), 5.20-5.10 (m, 2H), 4.60-4.55 (m, 1H), 2.70-2.50 (m, 2H), 2.30 (s, 3H), 2.45-1.70 (m, 7 H), 1.50-1.30 (m, 1H), 0.80 and 0.45 (s, 3H).

N-[1-(4-Chloro-phenyl)-but-3-enyl]-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (3.35c): white solid, isomer 1 ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 6.22 (d, J = 7 Hz, 1H), 5.72-5.63 (m, 1H), 5.26-5.18 (m, 2H), 4.60-4.55 (m, 1H), 2.68-2.62 (m, 2H), 2.60 (d, J = 18.5 Hz, 1H), 2.60-2.50 (m, 1H), 2.35-2.28 (m, 1H), 2.06-2.00 (m, 2H), 2.0-1.92 (m, 2H), 1.87 (d, J = 18.5 Hz, 1H), 1.40-1.38 (m, 1H), 0.81 (s, 3H), 0.50(s, 3H); ^{13}C NMR(125 MHz, $CDCl_3$): δ 217.08, 139.05, 133.53, 132.97, 128.75, 128.66, 118.68, 59.53, 57.66, 52.29, 48.57, 42.83, 42.49, 41.32, 27.63, 26.79, 19.36, 19.0; isomer 2: clear oil, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 5.66 (d, J = 7.0 Hz, 1H), 5.70-5.62 (m, 1H), 5.16-5.12 (m, 2H), 4.62-4.59 (m, 1H), 3.27 (d, J = 15 Hz, 1H), 2.85 (d, J = 15 Hz, 1H), 2.56 (2H, m), 2.44-2.40 (1H, m), 2.20-1.82 (m, 5H), 1.42-1.38 (m, 1H), 0.99 (s, 3H), 0.87 (s, 3H); ^{13}C NMR(125 MHz, $CDCl_3$): δ 216.25, 140.08, 133.13, 132.77, 128.66, 127.91, 119.38, 59.07, 56.78, 51.54, 48.40, 42.72, 42.64, 41.61, 26.77, 26.46, 19.74, 19.36.

C-(7,7-Dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-N-[1-(4-methoxy-phenyl)-but-3-enyl]-methanesulfonamide (3.35d): clear oil, ^{1}H NMR (200 MHz, $CDCl_3$): major isomer δ 7.30--7.20 (m, 2H), 6.90-6.80 (m, 2H), 6.18 (d, J = 8.0 Hz, 1H), 5.80--5.55 (m, 1H), 5.20-5.00 (m, 2H), 4.60-4.45 (m, 1H), 3.76 (s, 3H), 2.65-2.45 (m, 3H), 2.45-1.70 (m, 6 H), 1.50-1.30 (m, 1H), 0.78 and 0.45 (s, 3H); minor isomer 7.30--7.20 (m, 2H), 6.90-6.80 (m, 2H), 5.80--5.55 (m, 1H), 5.54 (d, J = 7.2 Hz, 1H), 5.20-5.00 (m, 2H), 4.60-4.45 (m, 1H), 3.79 (s, 3H), 3.22 and 2.75 (d, J = 18.5 Hz, 1H), 2.70-2.50 (m, 2H), 2.45-1.70 (m, 6 H), 1.50-1.30 (m, 1H), 1.10, 0.85 (s, 3H).

C-(2-Allyl-2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-N-[1-(4-methoxy-phenyl)-but-3-enyl]-methanesulfonamide (3.36): clear oil, mixture of isomers, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30--7.20 (m, 2H), 6.95-6.85 (m, 2H), 5.94-5.84 (m, 1H), 5.78--5.68 (m, 1H), 5.20-5.10 (m, 4H), 4.65(d, J = 8.0 Hz, 1H), 4.56-4.45 (m, 1H), 3.80 (s, 3H), 2.95-2.85 (m, 1H), 2.82 and 2.44 (d, J = 17.6 Hz, 1H), 2.60-2.54(m, 2H), 2.34 (minor) 2.18 (major) (s, 2H), 2.22-2.18 (m, 1H), 1.90-1.82 (m, 2H), 1.78-1.50 (m, 5H), 1.12-1.08 (m, 1H), 0.84 and 0.65 (major) (s, 3H), 0.95 and 0.45 (minor isomer) (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.29(159.27), 134.69 (134.65), 133.26(132.71), 128.29(128.23), 128.06(126.91), 119.21(119.16), 118.30, 118.11(118.01), 114.20(114.10), 56.77(56.49), 55.17(55.05), 54.56(54.39), 54.30, 51.61(51.60), 44.80(44.73), 44.15(44.09), 44.01(43.96), 41.47(41.40), 30.77, 27.77(26.81), 26.77(26.68), 20.76(20.73), 20.55(20.43).

3.6.6. Synthesis of menthol ester 3.43 [22]

a (1R, 2S, 5R) 2-isoPropyl-5-methyl-cyclohexyl bromo-acetate (3.39)

A mixture of (-)-menthol **3.37** (5g, 32 mmol), 1-bromoacetic acid **3.38** (11.2 g, 80 mmol), toluenesulfonic acid monohydrate (0.2 g) and benzene (80 mL) was heated at reflux for 24h with azeotropic removal of water and then cooled to room temperature and poured into saturated $NaHCO_3$ (200 mL). The aqueous phase was extracted with ether (3 X 20 mL). The combined organic layers were washed with brine, dried, and concentrated to afford the crude product **3.39**.

b. (1R, 2S, 5R) 2-isoPropyl-5-methyl-cyclohexyl (nitro-oxy)acetate (3.40)

The obtained bromoacetate ester **3.39** was dissolved in acetonitrile (100 mL), and $AgNO_3$ (16.3 g, 96 mmol) was added to the solution. The mixture was stirred at room temperature for 48 hr and concentrated at 30 °C. The residue was extracted with ether (3 X 30 mL). The combined organic layers were washed with brine, dried, concentrated, filtered through silica gel. Concentration of the filtrate afforded **3.40** (6.3 g, 76% yield). ^{13}C NMR (50 MHz, $CDCl_3$) 165.27, 68.33, 48.14, 41.94, 35.44, 32.84, 27.77, 24.87, 23.47, 22.25, 17.79.

c. (1R, 2S, 5R) 2-isoPropyl-5-methyl-cyclohexyl glyoxylate (3.42)

A mixture of nitrooxy acetate (2.59g, 10 mmol) and sodium acetate (820 mg, 10 mmol) dissolved in DMSO (80 mL) was stirred at room temperature for 1hr and then poured into ice salt water (150 mL). The solution was extracted with ether (5 X 20 mL). The combined organic layers were washed with brine, dried, and concentrated. The resulting liquid was distilled with P_2O_5 (1 g) under vacuum to afford **3.42** (80-85 °C/2 mmHg), which must be used immediately for the next step.

d. (Toluene-4-sulfonylimino)-acetic acid (1R, 2S, 5R)-2-isopropyl-5-methyl-cyclohexyl ester (3.43) To the solution of anhydrous and freshly distilled glyoxylic acid (-)-menthyl ester **3.41** (5 mmol) in dry benzene (20 mL), were added *p*-toluene-sulfonylisocyanate (5.5 mmol, 1.1 eq.) and catalytic amount of aluminum chloride (5% mol). The solution thus obtained was refluxed for 4 hr and the solvent was removed by distillation under vacuum until viscous oil was obtained as the expected product. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.88 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 4.96-4.80(m, 1H), 2.45 (s, 1H), 2.10-1.40 (m, 9H), 0.94-0.85 (m, 6H), 0.72 (d, 3H).

2-(Toluene-4-sulfonylamino)-pent-4-enoic acid (1R, 2S, 5R)-2-isopropyl-5-methyl-cyclohexyl ester (3.44) For experimental procedure, see section **3.6.3.** ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2, 2H), 7.25 (d, J = 8.2, 2H), 5.77-5.52 (m, 1H), 5.31 (t, 1H, J = 8,7 Hz), 5.19-5.03 (m, 2H), 5.05 (d, 1H, J = 1.64 Hz), 4.58-4.37 (m, 1H), 4.04-3.91 (m, 1H), 2.56-2.34 (m, 2H), 2.38 (s, 3H), 1.80-1.15 (m, 8H), 0.88-0.76 (m, 6H), 0.65-0.52 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): two isomers, 170.45(170.09), 143.56, 137.10, 131.59 (131.52), 129.95, 127.58 (127.47), 120.12, 78.60 (77.97), 56.45 (56.26), 47.92 (47.84), 41.82 (41.67), 39.44 (39.20), 35.39, 32.70(32.62), 27.63 (27.33), 24.81 (24.35), 23.55 (23.48), 23.12, 22.34(22.17), 17.78 (17.27).

3.6.7 Synthesis of chiral sulfinimine 3.48:

In a 50 mL round bottomed flask was added (-)-toluenesulfinic acid menthyl ester **3.45**[30] (2.0 g, 6.8 mmol) in THF (25 mL). The reaction mixture was cooled to –78 °C, and LiHMDS (10 mL, 1.0 M solution in THF, 10 mmol) was added dropwise via syringe.

The reaction mixture was stirred for 30 min before benzaldehyde was added dropwise. The reaction was warmed to room temperature, stirred for 1 h, and monitored for the disappearance of **3.45** by TLC. The reaction mixture was quenched with saturated NH_4Cl (20 mL) and the mixture was extracted with ethyl acetate (3 X 15 mL). The organic phase was dried (Na_2SO_4) and concentrated to give the crude product. Pure product was obtained as a crystalline solid by recrystallization (methylene chloride and hexane). mp: 76-78 °C(lit.[31] mp 77-78 °C), 90% ee $[\alpha]^{20}_D$ 107.5 (c, 1.35, $CHCl_3$), [lit. $[\alpha]^{20}_D$ 119.3 (c, 1.77, $CHCl_3$)]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.9-7.8 (m, 2H), 7.65 (d, J = 8 Hz, 2H), 7.50-7.34 (m, 3H), 7.25-7.35 (m, 2H), 2.40 (s, 3H).

4-Methyl-benzenesulfinic acid (1-phenyl-but-3-enyl)-amide (3.49). For the experimental procedure of allylation of **3.45**, see section **3.6.3**. Mixture of two isomers, white solid, ^{1}H NMR (200 MHz, $CDCl_3$): δ major isomer 7.65-7.05 (m, 9H), 5.78-5.55 (m, 1H), 5.18-5.10 (m, 2H), 4.55-5.45 (m, 1H), 4.40 (d, J = 8.0 Hz, 1H), 2.80-2.62 (m, 1H), 2.34 (s, 3H). minor isomer: 7.65-7.05 (m, 9H), 5.78-5.55 (m, 1H), 5.18-5.10 (m, 2H), 4.55-5.45 (m, 1H), 4.35 (br., 1H), 2.60-2.45 (m, 1H), 2.43 (s, 3H).

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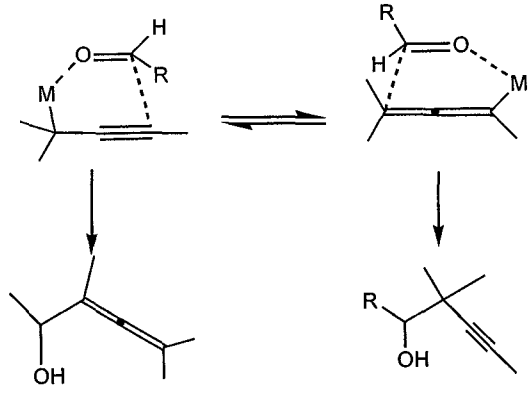
Chapter 4

Aqueous Addition Reaction of C=N Electrophiles. Propargylation *vs.* Allenylation

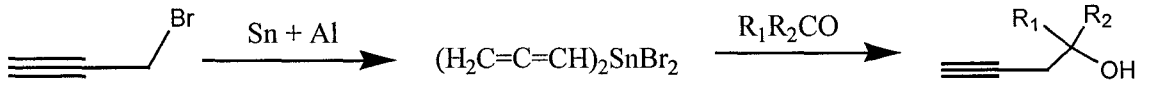
4.1 Introduction. An Overview of the Propargylic and Allenic Organometallics

The chemistry of acetylenes and allenes plays an important role in organic synthesis, as these structural units are present in a variety of natural products and biologically active compounds.[1] The alkynyl and allenic intermediates employed in these studies are frequently assembled by the nucleophilic addition of propargylic and allenic organometallics to carbonyl compounds. Just like allylation reaction of carbonyl electrophiles, a critical question for this reaction is the regioselectivity of the reaction that can lead to either homopropargylic or allenic adduct respectively.[2] (Scheme 4.1) In many cases, an equilibrium exists between the allenic and the propargylic organometallic reagents. The product distribution of the reaction is determined by the position of the equilibrium between the two organometallic intermediates and by their relative rates of addition to electrophiles.[3]



Scheme 4.1

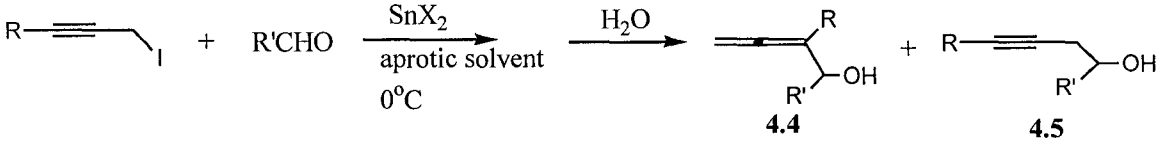
There have been extensive studies on the use of various propargylic or allenic organometallic reagents with an array of metals, such as magnesium,[4] lithium,[5] titanium,[6] zinc,[7] aluminum,[8] tin,[9] silicon[10] and boron[11] for this purpose. The regio- and chemo-selectivity of these organometallics on the nucleophilic addition have been examined. The regioselectivity seems to be primarily depended on the kind of metal used. It has been established that zinc, boron, tin, magnesium, and lithium show propargylic selectivity whereas aluminum exhibit allenic selectivity. An example is the preparation of diallenyltin dibromide (**4.2**) from the treatment of propargyl bromide (**4.1**) with metallic tin in the presence of metallic aluminum. Further reaction of diallenyltin dibromide (**4.2**) with carbonyl compounds gives homopropargylic alcohol **4.3** selectively.[12] (Scheme 4.2) Interestingly, this selectivity is different from a previous report by Mukaiyama and Harada, who found the α-allenic alcohol to be the major product from propargyltin reagent prepared from a tin(II) halide.[13] (Scheme 4.3)



4.1 **4.2** **4.3**

benzaldehyde	94%
heptanal	77%
cyclohexanone	90%

Scheme 4.2



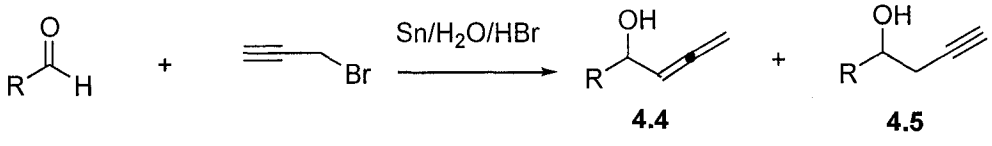
4.4 **4.5**

		yield%	**4.4:4.5**
R=H	Benzaldehyde	98	48:52
	$PhCH(CH_3)CHO$	95	60:40
	$n\text{-}C_8H_{17}CHO$	92	70:30

Scheme 4.3

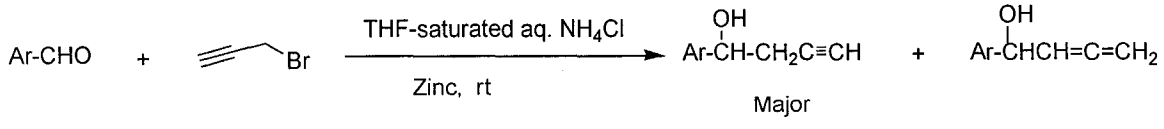
Organometallic reactions in aqueous media have attracted considerable attention recently. In the previous chapters, we have discussed the aqueous Barbier-type allylation reaction with electrophiles.[14] On the other hand, there is a parallel interest in examining the reactions of propargylic and allenic organometallics in aqueous media.

Under the Barbier-type reaction conditions, such coupling can be realized in aqueous media. However, the initial results showed poor regioselectivity. For example, Wu[15] *et al* examined the coupling reaction between propargyl bromide with aldehydes mediated by tin in aqueous media. (Scheme 4.4) The reaction was found to give a mixture of homo-propargylic and allenic alcohols (**4.4** and **4.5**) in nearly equal proportions and thus the reaction showed less synthetic potential.



Scheme 4.4

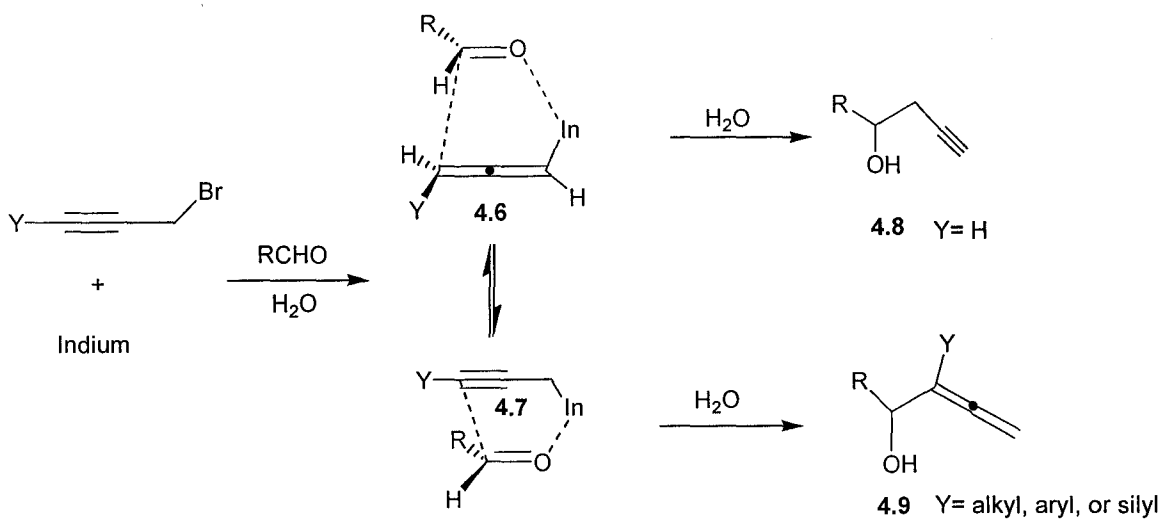
Yavari[16] *et al* reported that in the presence of metallic zinc, propargyl bromide was found to react with aldehydes at room temperature in a mixture of THF and aqueous saturated ammonium chloride (5:2) to afford the corresponding homo-propargylic alcohols in moderate to high yields together with small amount of α-allenic alcohols.(Scheme 4.5)



Scheme 4.5

Chan and Isaac[17] carried out a more systematic study. By using indium for this coupling in aqueous media, they found that the regioselectivity of the reaction critically

depended on the propargyl bromides used. Unsubstituted propargyl bromides led to the acetylene products (**4.8**) predominantly while γ-substituted propargyl bromides gave mostly allenic products (**4.9**). (Scheme 4.6) For example, the indium-mediated reaction of nonanal with 3-bromo-propyne (Table 4.1, *entry 1*) or 1-bromo-but-2-yne (*entry 3*) showed completely different selectivity in the reaction.



Scheme 4.6

Table 4.1 Selected examples in the indium-mediated coupling of prop-2-ynyl systems with aldehydes in water

Entry	Aldehydes R=	Prop-2-ynyl bromides	Combined yields(%)	allene: acetylene **4.9** **4.8**
1	n-C_8H_{17}	$BrCH_2CCH$	97	12:88
2	n-C_8H_{17}	$BrCH_2CCPh$	89	95:5
3	n-C_8H_{17}	$BrCH_2CCMe$	99	100:0
4	n-C_8H_{17}	$BrCH_2CCSiMe_3$	82	67:33
5	1-napthyl	$BrCH_2CCH$	50	10:90
6	1-napthyl	$BrCH_2CCMe$	98	100:0
7	1-napthyl	$BrCH_2CCSiMe_2Ph$	70	80:20

To account for such regioselectivity, it is assumed that an equilibrium exits between the propargylic indium **4.7** and the allenic indium **4.6** formed *in situ* from the reaction of propargyl bromide and indium metal. In the case of non-substituted propargyl bromide, the reaction rate of the allenic indium species **4.6** with aldehyde is faster than the corresponding propargylic indium species and therefore the acetylene product **4.8** predominates. On the other hand, when the γ position was substituted, the reaction rate of the allenic indium species **4.6** with electrophiles is hampered by the influence from the substituent and therefore the reaction of the propargylic indium species with electrophiles is favored leading to the formation of the α-allenic alcohols **4.9** as the major product.

In the study of the total synthesis (+)-Goniofuturone, Li's group has performed an investigation on the role of different metals on the aqueous propargylation *vs* allenylation of aldehydes.[18] The reaction of propargyl bromide with benzaldehyde mediated by indium at room temperature in aqueous methanol was found to be fairly regioselective with a preference for the formation of the homopropargyl alcohol. On the other hand, the same reaction mediated with tin or bismuth provided slightly lower selectivity. The use of zinc further lowered the selectivity while the use of cadmium had no selectivity on the product formation. (Table 4.2) The reaction of heptaldehyde with propargyl bromide in aqueous methanol mediated by indium, bismuth, or cadmium all gave low selectivity, while mediation by tin or zinc showed slightly higher selectivity favoring the propargylation product.

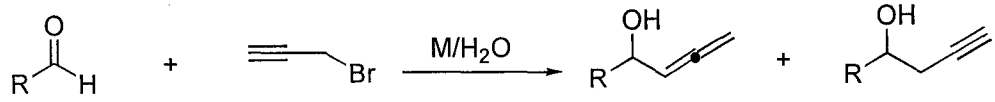


Table 4.2 Effect of Metals on the Propargylation-Allenylation Reaction

entry	R	metal	Allenylation/ Propargylation	Overall yield %
1	Phenyl	In	1:6	72
2	n-hexyl	In	1:2	85
3	Phenyl	Sn	1:5	60
4	n-hexyl	Sn	1:6	60
5	Phenyl	Zn	1:3	64
6	n-hexyl	Zn	1:4.4	65
7	Phenyl	Bi	1:5	83
8	n-hexyl	Bi	1:1	60
9	Phenyl	Cd	1:1	60
10	n-hexyl	Cd	1:1	20

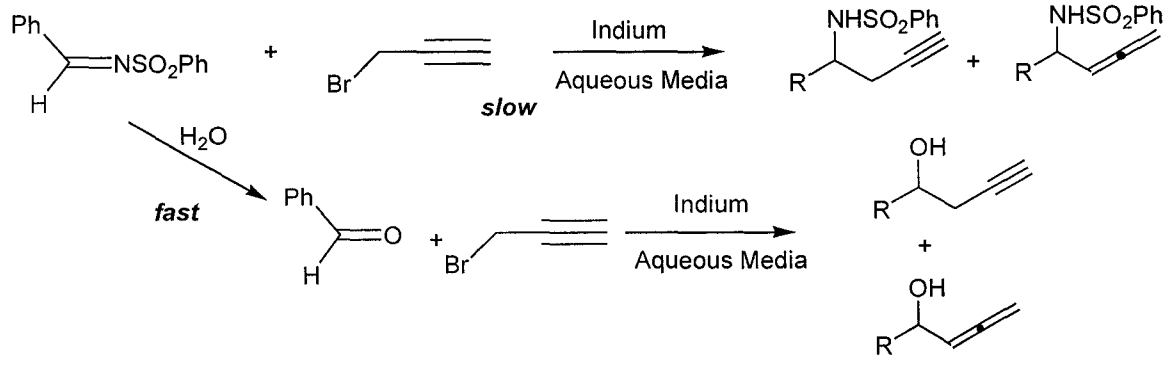
4.2 Propargylation *vs.* Allenylation of Sulfonimines in Aqueous Media

4.2.1 Preliminary Study with Indium

Although there have been extensive studies on the aqueous nucleophilic addition of propargylic or allenic organometallic reagents, the study is limited to carbonyl compounds. Few attempt has been reported to extend this methodology to C=N electrophiles in aqueous media. Presumably, the reasons are associated with the low electrophilicity and aqueous instability of C=N electrophiles. In the previous chapters,

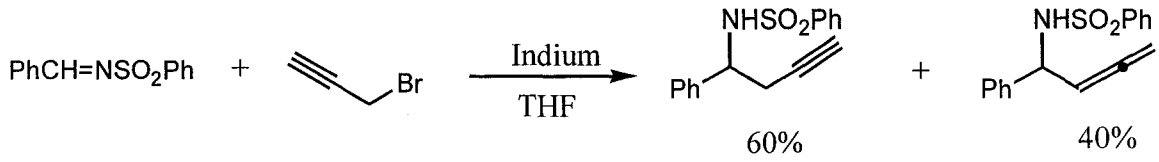
we have demonstrated that sulfonimines can be employed as a useful C=N electrophile in aqueous media due to the stronger electrophilic character and water stability. The success of the coupling reaction with allylmetal in aqueous media encouraged us to examine the aqueous reaction of sulfonimines with propargylic or allenic organometals.

The initial investigation on this reaction with indium was rather disappointing. In aqueous media, the coupling of propargyl bromide with sulfonimines mediated by indium gave propargylic alcohols instead of the expected sulfonamide, presumably due to the prior hydrolysis of the sulfonimines in aqueous media, although allylation reaction of sulfonimines can proceed under similar conditions. We attributed the failure to the relatively low reactivity of the propargylic or allenic indium species comparing to allylindium(I) intermediate. Therefore, the hydrolysis of the sulfonimines is faster than the anticipated transformation, and the propargylic or allenic alcohol was obtained instead. The attempt to minimize the hydrolysis by using a mixture of THF and water (10:1) as solvent was still not successful.[19]



Scheme 4.7

However, the reaction can be performed in pure THF alone to give the products. The regioselectivity was poor with a ratio of homopropargylic product and allenic product around 3:2. (Scheme 4.8)



Scheme 4.8

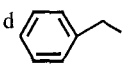
4.2.2 Screening of Metals

We therefore engaged in screening an array of metals for the reaction. The reaction of benzenesulfonimine with propargyl bromide was used as the model reaction for this study and the results were summarized in Table 4.3. Most of the metals did not give the expected coupling reaction. However we were quite pleased to find that zinc powder in saturated ammonium chloride was quite efficient in mediating the propargylic addition of sulfonimines in water. The reaction showed excellent regioselectivity giving the homopropargylic sulfonamide exclusively. Due to the excess amount of zinc powder used, small amount of the reduction product was observed. However, to our knowledge, this is the first example of performing propargylation reaction of C=N electrophiles in aqueous media.

Table 4.3 The Screening of the Metals for the Propargylation of Benzylsulfonimine in Aqueous Media

Entry	Media	Metal (eq.)	Yield%[a]
1	THF	In (2)	67 (3:2 propargylation product to allenyl product.)
2	THF:H_2O (9:1)	In (2)	___[b]
3	H_2O	Sn(1.5) Al(cat.)	___[b]
4	H_2O	Bi (1.5) TBAF (1.5)	___[b]
5	NH_4Cl/H_2O	Zn (2)	20[c]
6	NH_4Cl/H_2O	Zn (4)	38[c]
7	NH_4Cl/H_2O	Zn (6)	65 (sulfonimine was totally consumed after 4 hr. 16% of reduced sulfonamide in crude product.)
8	K_2HPO_4/H_2O	Zn (6)	18[d]
9	KH_2PO_4/H_2O	Zn (6)	trace
10	KH_2PO_4/K_2HPO_4(1:1)/H_2O	Zn (6)	32[d]
11	NaH_2PO_4/H_2O	Zn (6)	28[d]

[a] Isolated yields. [b] Starting materials and reduction products were recovered.

[c] Sulfonimine was not totally consumed. [d]  was the major product.

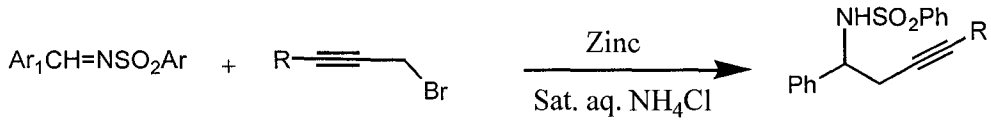
4.2.3 Zinc-Mediate Propargylation Reaction of Sulfonimines in Aqueous Media

It could be seen in Table 4.4 that, mediated by zinc in saturated aqueous NH_4Cl solution, various homopropargylic sulfonamides could be prepared by the addition reaction of propargylic bromides and sulfonimines. Unlike the indium-mediated reaction in THF, the reaction showed excellent regioselectivity giving homopropargylic product exclusively. In most cases, moderate yields were obtained due to the competing reduction of the sulfonimines by zinc.

The mechanism for the zinc mediated Barbier-type propargylation is still not clear. However, in comparison with carbonyl compounds, the exclusively propargylic selectivity in sulfonimines may imply that sulfonimines may also play a role on the regioselectivity of the reaction. It has been suggested that in the metal-mediated aqueous Barbier-type reaction, different metals may proceed by different mechanism. In the case of zinc, no organozinc intermediate has been observed in aqueous media. It is likely that similar to Mg, the zinc-mediated aqueous reactions might go through an SET process on the metal surface involving radical intermediate.[20] Therefore, in comparison with tin or indium, zinc seems to be more reactive in many cases.[21]

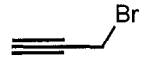
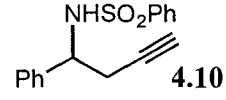
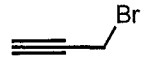
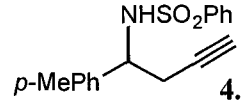
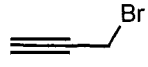
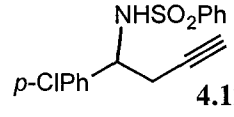
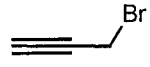
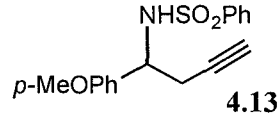
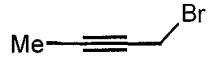
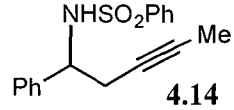
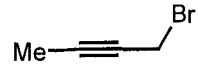
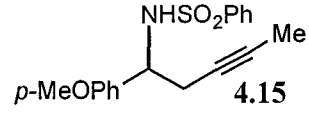
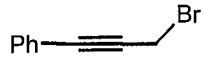
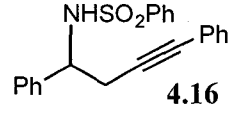
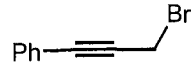
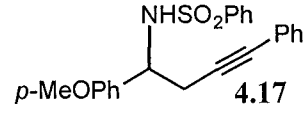
4.3 Conclusion

Aqueous addition reaction of sulfonimines with propargyl/allenyl organometallics was investigated. By screening an array of metals under various conditions in aqueous media, zinc was found to be the metal of choice for mediation of the Barbier-type propargylation of sulfonimines in saturated aqueous NH_4Cl. The reaction showed exclusive regioselectivity giving the homopropargylic sulfonamides in moderate yields.



exclusively

Table 4.4 Propargylation of sulfonimines mediated by zinc in sat. NH_4Cl aqueous media.

Entry	Sulfonimine	Propargyl Bromide	Product	Yield%[a]
1	PhCH=NSO$_2$Ph		 **4.10**	65
2	*p*-MePhCH=NSO$_2$Ph		 **4.11**	38
3	*p*-ClPhCH=NSO$_2$Ph		 **4.12**	40
4	*p*-MeOPhCH=NSO$_2$Ph		 **4.13**	52
5	PhCH=NSO$_2$Ph		 **4.14**	45
6	*p*-MeOPhCH=NSO$_2$Ph		 **4.15**	36
7	PhCH=NSO$_2$Ph		 **4.16**	40
8	*p*-MeOPhCH=NSO$_2$Ph		 **4.17**	32

[a] Isolated yields.

4.4 Experimental Section

General Aspect: see Chapter 2, Experimental Section.

General Procedure:

To a vigorously stirred mixture of sulfonimine (0.5 mmol, 1eq.) and propargyl bromide (1 mmol, 2eq.) in saturated NH_4Cl aqueous solution (4 mL), zinc powder (3 mmol, 6 eq.) was added all at once. The mixture was stirred for 4 h and quenched by adding 1N HCl (2 mL). The aqueous phase was washed by ether (3 × 20 mL). The combined organic phase was washed with Na_2CO_3 saturated aqueous solution and brine respectively, and dried over Na_2SO_4. The product was obtained via silica gel flash column chromatography, with 10~15 % ethyl acetate in hexane as eluent.

N-(1-Phenyl-but-3-ynyl)-benzenesulfonamide (4.10) Colorless oil, IR (neat, cm^{-1}), 2785.8, 1324.3, 1160.9, 1091.2; ^1H NMR (400 MHz, $CDCl_3$): 7.76-7.72 (m, 2H), 7.50-7.44 (m, 1H), 7.42-7.38 (m, 2H), 7.20-7.18 (m, 3H), 7.28-7.25 (m, 2H), 5.14 (d, J = 7.2 Hz, 1H), 4.54 (dt, J = 6.4, 6.4 Hz, 1H), 2.65 (2H, dd, J = 6.4, 2.2 Hz), 1.99 (1H, dd, J = 2.8, 2.0Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 140.45, 139.19, 132.80, 129.09, 128.73, 128.22, 127.33, 126.76, 79.18, 72.52, 55.91, 27.51; MS (EI) 285 (M^+, 1.6), 246 (100); HRMS (FAB): calcd $C_{16}H_{15}NO_2S + H^+$ 286.0902, found 286.0902.

N-(1-p-Tolyl-but-3-ynyl)-benzenesulfonamide (4.11), colorless oil, ^1H NMR (300 MHz, $CDCl_3$): 7.78-7.72 (m, 2H), 7.56-7.48 (m, 1H), 7.42-7.37 (m, 2H), 7.08 (s, 4H), 5.14 (d, 1H, J = 6.4 Hz), 4.48 (dt, 1H, J = 6.3, 6.3 Hz), 2.63 (dd, 2H, J = 2.7, 6.0 Hz), 2.28 (s, 3H), 1.97 (dd, 1H, J = 2.4, 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 140.50, 137.98, 136.29, 132.72, 129.07, 127.36, 126.67, 79.40, 76.82, 72.32, 55.78, 27.47, 21.27; MS

(FAB) 300 (M^++H, 6.5), 260 (34), 105(100); HRMS (FAB): calcd $C_{17}H_{17}NO_2S$ + H^+ 300.1058, found 300.1059.

N-[1-(4-Chloro-phenyl)-but-3-ynyl]-benzenesulfonamide (4.12): white solid, IR (neat, cm^{-1}), 1445.7, 1320.1, 1155.8, 1090.6; ^1H NMR (300 MHz, $CDCl_3$): 7.85-7.78 (m, 2H), 7.53-7.48 (m, 3H), 6.96(d, 2H, J = 7.8 Hz), 6.68 (d, 2H, J = 7.8 Hz), 5.46 (d, 1H, J = 7.0 Hz), 4.53 (dt, 1H, J = 6.2, 6.2 Hz), 2.62 (dd, 2H, J = 6.2, 2.4 Hz), 1.97 (dd, 1H, J = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 146.45, 142.29, 131.81, 129.09, 128.78, 128.56, 127.83, 127.75, 79.68, 72.58, 56.11, 27.44; MS (EI) 320 ($M+H^+$, 2.1), 124(100); HRMS (FAB): calcd $C_{16}H_{14}ClNO_2S$ + H^+ 320.0512, found 302.0513.

N-[1-(4-Methoxy-phenyl)-but-3-ynyl]-benzenesulfonamide (4.13) colorless oil, IR (neat, cm^{-1}), 1611.9, 1514.3, 1447.4, 1323.4, 1160.1830.2; ^1H NMR (200 MHz, $CDCl_3$): 7.78-7.70 (m, 2H), 7.48-7.36 (m, 3H), 7.08-7.02(d, 2H), 6.72-6.68 (d, 2H), 5.22 (d, 1H, J = 7.0 Hz), 4.47 (dt, 1H, J = 6.2, 6.2 Hz), 3.75 (s, 3H), 2.62 (dd, 2H, J = 6.2, 2.4 Hz), 1.97 (dd, 1H, J = 2.6 Hz); ^{13}C NMR (75MHz, $CDCl_3$): 159.51, 140.68, 132.67, 131.42, 129.04, 128.00, 127.35, 114.11, 79.47, 72.28, 55.58, 55.46, 27.49; MS (EI) 354 (M^+, 0.2), 276 (100); HRMS (FAB): calcd $C_{17}H_{17}NO_3S$ + K^+ 354.0566, found 354.0567.

N-(1-Phenyl-pent-3-ynyl)-benzenesulfonamide (4.14) white solid, IR (neat, cm^{-1}): 3278, 3060, 1959, 1448, 1327, 1164, 929; ^1H NMR (300 MHz, $CDCl_3$): 7.72-7.66 (m, 2H), 7.48-7.43 (m, 1H), 7.38-7.32 (m, 2H), 7.20-7.10(m, 5H), 5.24 (d, 1H, J = 7.5 Hz), 4.82-4.74 (m, 2H), 4.74-4.66 (m, 1H), 1.47 (t, 3H, J = 3.3 Hz); ^{13}C NMR (75MHz, $CDCl_3$): 140.93, 139.02, 132.51, 128.88, 128.68, 128.09, 127.55, 127.27, 100.27, 79.24,

59.37, 16.36; MS (FAB) 300 ($M+H^+$, 2.58), 246 (100); HRMS (EI): calcd $C_{17}H_{17}NO_2S$ 299.0980, found 299.0983.

N-[1-(4-Methoxy-phenyl)-pent-3-ynyl]-benzenesulfonamide (4.15) colorless oil, IR (neat, cm^{-1}): 2836, 1955, 1607, 1512, 1447, 1324, 1251, 1161, 1032; ^1H NMR (300 MHz, $CDCl_3$): 7.70-7.67 (m, 2H), 7.50-7.44 (m, 1H), 7.40-4.32 (m, 2H), 7.05 (d, 2H, J = 6.6 Hz), 6.71 (d, 2H, J = 6.6 Hz), 5.07 (d, 1H, J = 5.4 Hz), 4.84-4.78 (m, 1H), 4.74-4.68 (m, 2H), 3.75 (s, 3H), 1.46 (t, 3H, J = 2.4 Hz); ^{13}C NMR (75MHz, $CDCl_3$): 159.44, 141.01, 132.46, 131.05, 128.86, 128.82, 127.29, 114.03, 100.46, 79.33, 58.73, 55.49, 16.47; MS (FAB) 329 (M^+, 2.58), 276 (100); HRMS (EI): calcd $C_{18}H_{19}NO_3S + H^+$ 329.1086, found 329.1083

N-(1,2-Diphenyl-but-3-ynyl)-benzenesulfonamide (4.16)

^1H NMR (400 MHz, $CDCl_3$): 7.79-7.76 (m, 2H), 7.48-7.43 (m, 1H), 7.40-7.18 (m, 12H), 5.27(d, 1H, J = 7.2 Hz), 4.60 (dt, 1H, J = 6.0, 6.0 Hz), 2.85 (dd, 2H, J = 6.0, 4.8 Hz); ^{13}C NMR (75MHz, $CDCl_3$): 140.44, 139.58, 132.73, 131.87, 129.08, 128.68, 128.50, 128.48, 128.14, 127.33, 126.81, 122.99, 84.54, 84.48, 56.48, 28.71; MS (EI) 362 (M^++1, 7.4), 246 (63), 77 (100); HRMS (FAB): calcd $C_{22}H_{19}NO_2S + H^+$ 362.1215, found 362.1213.

N-[1-(4-Methoxy-phenyl)-2-phenyl-but-3-ynyl]-benzenesulfonamide (4.17) white solid, ^1H NMR (300 MHz, $CDCl_3$): 7.78-7.74 (m, 2H), 7.54-7.22 (m, 8H), 7.11 (d, 2H), 6.68 (d, 2H), 5.19 (d, 1H, J = 6.3 Hz), 4.54 (dt, 1H, J = 6.0, 6.0 Hz), 3.77 (s, 3H), 2.83 (d, 2H, J = 6.0 Hz); ^{13}C NMR (75MHz, $CDCl_3$): 159.44, 140.51, 132.70, 131.87, 131.72, 129.07, 128.50, 128.48, 128.02, 127.35, 123.02, 114.05, 84.73, 84.39, 55.97, 55.51,

28.69, MS (EI) 430 (M^++K, 4.7), 276 (76), 55(100); HRMS (FAB): calcd $C_{23}H_{21}NO_3S$ + K^+ 430.0879, found 430.0880.

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[21] We have also observed a similar situation in the zinc-mediated aqueous allylation reaction of sulfinimine while other metals such as tin or indium could not mediate the reaction. *See:* sections 3.4.3

Chapter 5

Beyond the Boundary of Allylation Transformations. Other Possible Organometallic Carbon-Carbon Bond Forming Reactions in Aqueous Media

5.1 Introduction

Since water has been explored as an alternative solvent in organic chemistry in 1980's, aqueous organometallic reactions including the aqueous Barbier-type allylation reaction of carbonyl compounds have been developed. Extensive study has been carried out on the reactivity, mechanism and stereocontrol of the Barbier-type allylation reaction. The methodologies have been widely applied in the synthesis of carbohydrates and other natural products.[1] However, this chemistry was mostly confined to allylic and related transformations. In order to render the aqueous organometallic reaction a versatile and useful methodology, it is imperative to expand the scope of the aqueous Barbier-type reactions to more organic transformations.

In the Barbier-type reactions, the organometallic reagents, which are generated *in situ* from metal with halides, react with electrophiles leading to the final products. In the allylation reaction, allyl bromide or its derivatives were applied in the reaction and allylmetal intermediates were presumably generated.[2] Three basic issues for performing the aqueous Barbier-type reactions need to be considered. (i) Could the organometallic reagents or intermediates be generated in aqueous media under the Barbier-type

conditions? (ii) Could the generated organometallic intermediates be stable enough to survive in aqueous environment for further reactions with the substrates? (iii) Could the generated organometallic intermediates be reactive enough for further reactions with the electrophiles? Actually, the last two issues are interrelated. On the one hand, the generated organometallic intermediate should be stable enough to survive the aqueous media; on the other hand, they should be reactive enough for the nucleophilic addition with the substrates.

It has been generally accepted that the stability of an organometallic species generally increases with the decreasing ionic nature of the carbon-metal bond and thus with the decreasing difference of electronegativity between the metal center and the carbon atom.[3] (Figure 5.1)

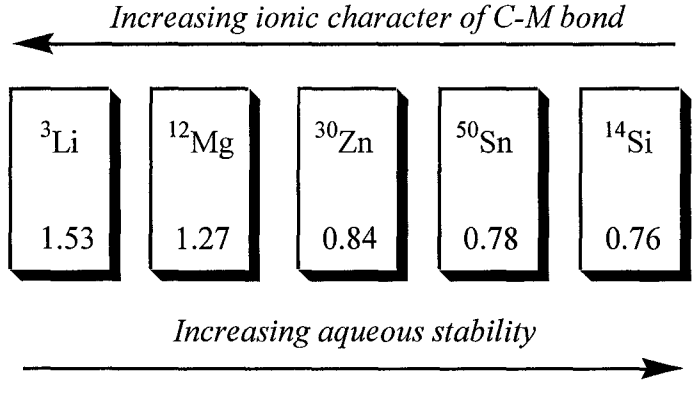
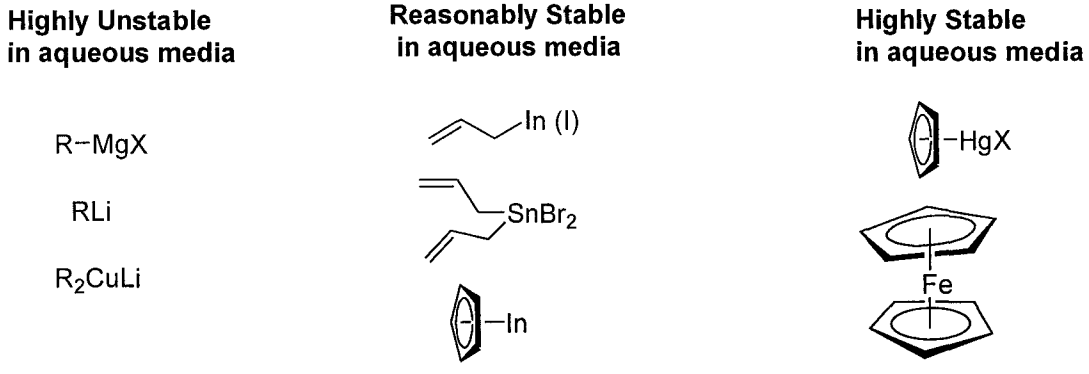


Figure 5.1 Metals used for the formation of organometallic complexes and electronegativity difference between the metal and carbon (by Allred-Rochow electronegativity scale)

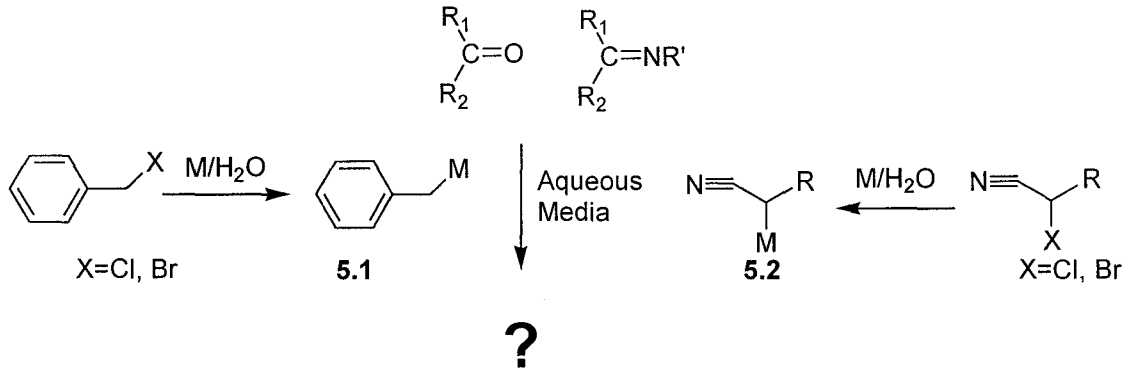
As a result, the organometallic compounds with high ionic metal-carbon bond, such as organoalkali reagents usually cannot survive in aqueous media. For example, the

Grignard or organolithium reagents should be handled under strictly anhydrous conditions. On the other hand, when the metal-carbon bond is less ionic, the aqueous stability of the organometallic compounds can be enhanced. This can partially account for the reasonable stability of some allylmetal species in aqueous media that lead to the metal-mediated aqueous allylation reaction with carbonyl compounds. At the extreme end of the spectrum, some cyclopentadienyl sandwich or half-sandwich heavy transition metal compounds such as cyclopentadienyl mercury chloride and ferrocene have high stability in water and are inert to most electrophiles. (Scheme 5.1)



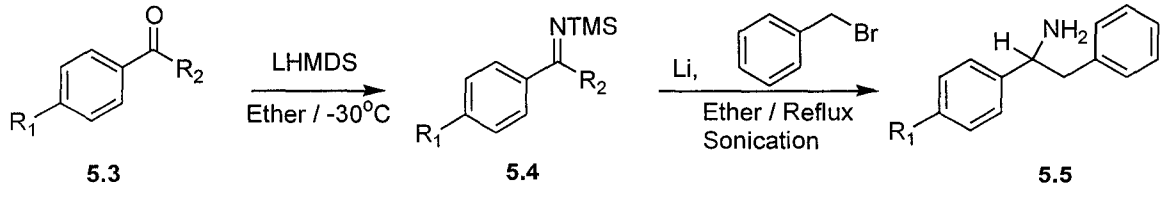
Scheme 5.1

On the other hand, the structural features of the bromides are also critical for stabilizing the generated organometallic reagents in aqueous media. A proximal functional group that could either disperse the electron density (such as allyl or benzyl group) or chelate with the metal atom would be essential for the enhancement of the aqueous stability. At the same time, such aqueous stability enhancement should not be at the cost of reducing the nucleophilicity of the generated organometallic reagents. With these considerations, we have examined the use of benzyl bromide and α-bromoacetonitrile derivatives in the aqueous metal-mediated Barbier-type reactions. (Scheme 5.2)

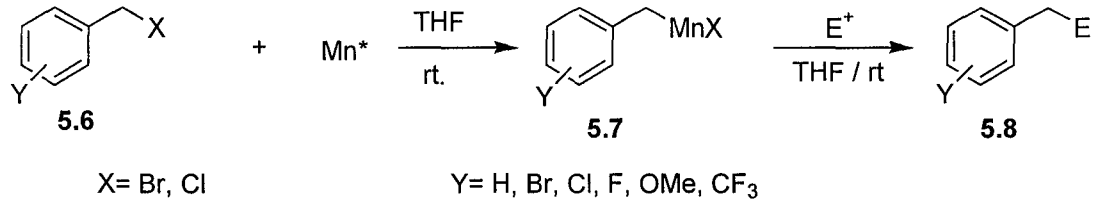


Scheme 5.2

Benzylation of carbonyl compound is an important organic transformation in organic synthesis. Benzylmetallic reagents were generally employed for the addition of carbonyl compounds to give the corresponding alcohols.[4] The Barbier-type reaction has been demonstrated to be an efficient way to generate benzylmetallic regents for the benzylation reaction. For example, (trimethylsilyl)imines **5.4** prepared *in situ* have been found to react with benzyl bromide in the presence of lithium metal upon sonication to give primary amines **5.5** in fair to good yield.[5] (Scheme 5.3) Activated manganese was also found to generate the presumed benzylmanganese chloride species **5.7** for the addition reaction with electrophiles[6] (Scheme 5.4). It should be pointed out that all these reactions had to be performed under strictly anhydrous conditions.

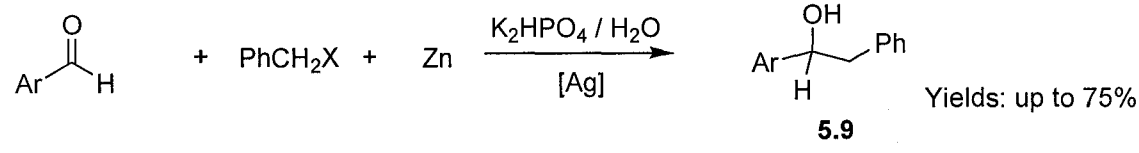


Scheme 5.3



Scheme 5.4

Recently, Bieber's group reported an interesting observation of the promoting effect of inorganic salts on the aqueous Barbier-type reactions. They firstly reported the promotion effect of silver salts in the aqueous zinc-mediated Reformatsky reaction.[7] Later, they found that silver salt could also catalyze the zinc-mediated Barbier-type benzylation of carbonyl compounds in water.[8] (Scheme 5.5)



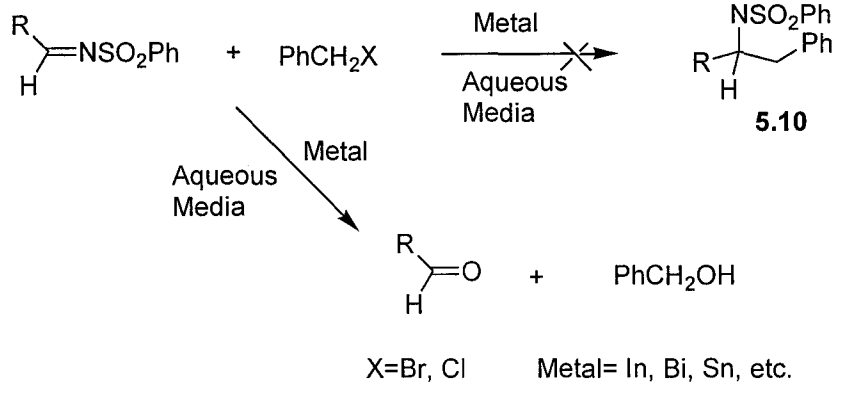
Scheme 5.5

5.2 Aqueous Barbier-type Benzylation Reaction of Sulfonimines

It has been demonstrated in the previous chapters that by using sulfonimine as an activated C=N electrophile, the aqueous Barbier-type allylation and propargylation reactions can be smoothly carried out.[9] In this chapter, we are going to examine if these electrophiles can also be employed in aqueous benzylation reactions, and hence, to expand the scope of the Barbier-type transformation in aqueous media.

However, preliminary investigation of the indium-mediated benzylation of sulfonimines was unsuccessful. Benzaldehyde from the hydrolysis of its

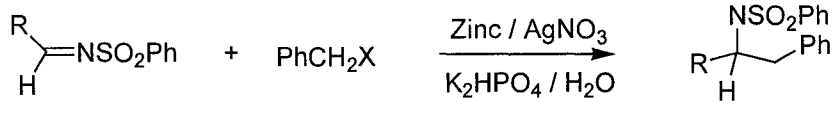
benzenesulfonimine was observed as the major product. Benzyl alcohol was also obtained due to the hydrolysis of benzylbromide. Trace amount of the pinnacol coupling product from benzaldehyde and the Wurtz coupling product from benzyl bromide were also observed. The screening of other metals including tin, bismuth and manganese for this purpose was also performed. However, few encouraging results were obtained and the results were similar to the case of using indium. (Scheme 5.6)



Scheme 5.6

To our delight, under the Biebier's conditions by using of zinc, benzylation of sulfonimines could be performed smoothly in aqueous media giving the corresponding benzyl sulfonamides in moderate to good yields. (Scheme 5.7) The reaction worked equally well for both aromatic and aliphatic sulfonimines. (Table 5.1) However, with hindered sulfonimines, the benzylation reaction could not proceed and only hydrolyzed aldehydes were recovered (Table 5.1, *entry 8*). Unlike the indium mediated aqueous allylation reaction of sulfonimines, electron-donating substituent on the benzene ring, which actually reduced the electrophilicity of the C=N bond, enhanced the yield of the

reaction, while electron-withdrawing group on the substrate led to reduced yield (*entries 2 and 4*). Either electron-withdrawing or electro-donating substitution on the benzyl chloride decreased the reactivity of the organometallic intermediates produced *in situ,* and as a result, decreased yields were obtained (*entries 9~11*). The corresponding benzyl alcohols were the major side products in these cases. The use of benzyl bromide instead of chloride led to a reduced yield (*entry 1*).

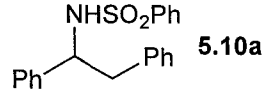
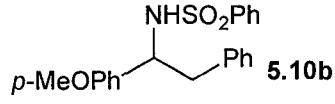
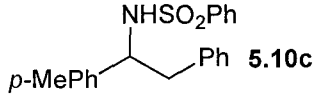
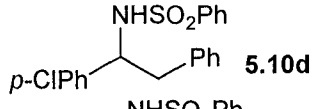
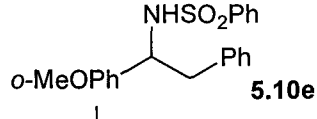
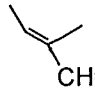
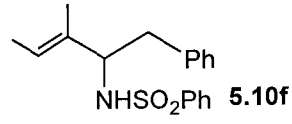
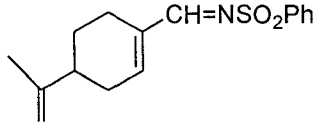
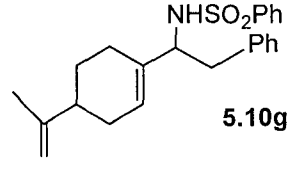
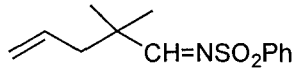
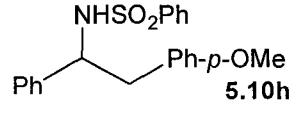
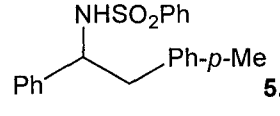
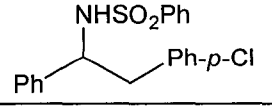


5.10

Scheme 5.7

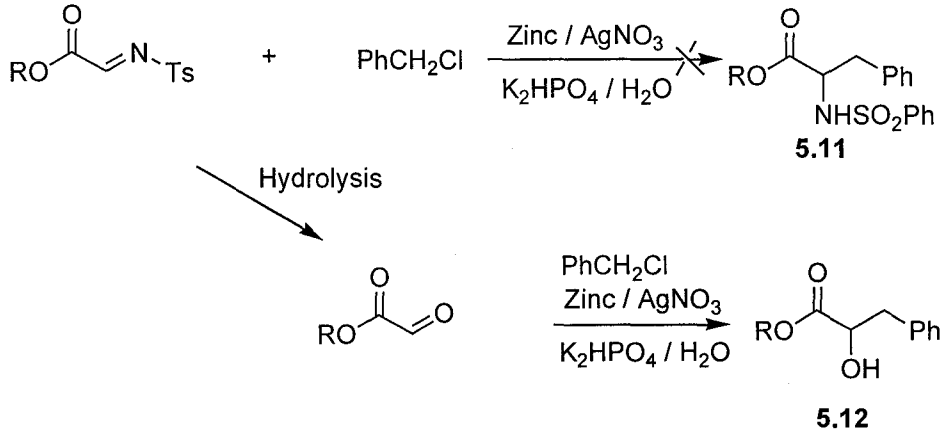
At this stage, we cannot conclude a clear mechanism for this zinc-mediated aqueous benzylation reaction. However, the unique promotion effect of inorganic silver salt implied that the zinc-mediated aqueous Barbier-type reaction may undergo a different process from the indium or tin-mediated aqueous organometallic reactions in which organoindium or organotin intermediates were usually involved. The SET (single electron transfer) process proposed by Li[10] may be more suitable for accounting for the results.

Table 5.1 Benzylation reaction of sulfonimines in Aqueous Media

Entry	Sulfonimine	Benzyl Halide	Product	Yields(%)[a]
1	$PhCH{=}NSO_2Ph$	$PhCH_2Cl$	 **5.10a**	59
		$PhCH_2Br$		15
2	*p*-$MeOPhCH{=}NSO_2Ph$	$PhCH_2Cl$	 **5.10b**	78
3	*p*-$MePhCH{=}NSO_2Ph$	$PhCH_2Cl$	 **5.10c**	69
4	*p*-$ClPhCH{=}NSO_2Ph$	$PhCH_2Cl$	 **5.10d**	37
5	*o*-$MeOPhCH{=}NSO_2Ph$	$PhCH_2Cl$	 **5.10e**	61
6		$PhCH_2Cl$	 **5.10f**	52
7		$PhCH_2Cl$	 **5.10g**	55
8		$PhCH_2Cl$	——	0
9	$PhCH{=}NSO_2Ph$	*p*-$MeO\text{-}PhCH_2Cl$	 **5.10h**	25
10	$PhCH{=}NSO_2Ph$	*p*-$Me\text{-}PhCH_2Cl$	 **5.10i**	24
11	$PhCH{=}NSO_2Ph$	*p*-$Cl\text{-}PhCH_2Cl$	 **5.10j**	20

[a] Isolated yields.

Unfortunately, the attempt of aqueous benzylation reaction of sulfonimino-acetic acid ester was unsuccessful. The reaction may potentially provide a novel approach for the synthesis of phenylalanine. The failure of this reaction may probably due to the relative low aqueous stability of sulfonimino-acetic acid ester compared with other sulfonimines, and as a result, the corresponding benzylated alcohol **5.12** was obtained instead of the desired sulfonamide **5.11** (Scheme 5.8). This is in agreement with the previous observation that electron-withdrawing group may enhance the hydrolysis of sulfonimine and lead to reduced yield of the aqueous benzylation reaction.

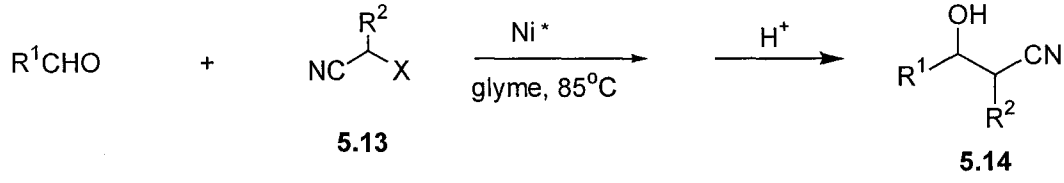


Scheme 5.8

5.3 Metal-Mediated Coupling Reaction of α-Bromoacetonitrile and Aldehydes in Aqueous Media

The coupling reaction of α-bromoacetonitriles with aldehydes is another important reaction for carbon-carbon bond formation especially for the synthesis of heterocycle compounds in the synthesis of natural products.[11] This reaction can be regarded as a variation of the Reformatzky reaction. The first realization of this addition was mediated

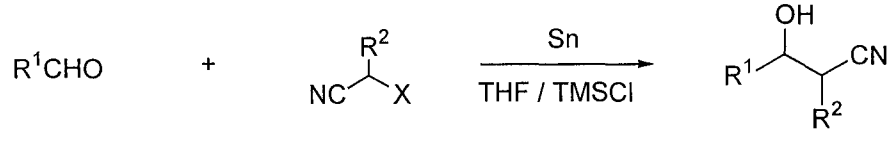
by metallic nickel.[12] β-Hydroxynitriles **5.14** were prepared by the addition of α-haloacetonitriles **5.13** to aldehydes in the presence of metallic nickel generated *in situ* from the reduction of nickel iodide with lithium in glyme. (Scheme 5.9)



5.13 **5.14**

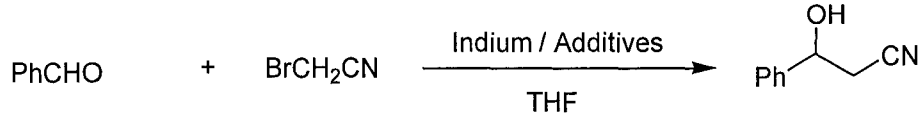
Scheme 5.9

Later, it was found that the reaction could be performed under the mediation of zinc,[13] tin[14], SmI_2[15], or cobalt-phosphine. In each case, either additive or high temperature seemed to be critical for the reaction to proceed. For example in the tin-mediated coupling reaction, TMSCl was necessary for the promotion of the reaction. (Scheme 5.10)



Scheme 5.10

Indium-mediated coupling reaction of bromoacetonitrile with carbonyl compounds was also reported by Araki *et al.*[16] The organoindium reagent, derived *in situ* from the reaction of indium metal with bromoacetonitrile in organic solvent, reacted with carbonyl compounds in the presence of chlorotrimethylsilane to give β-hydroxynitriles. (Scheme 5.11) Additives were found to be essential for the reaction. The effect of various additives was carefully examined in their work.



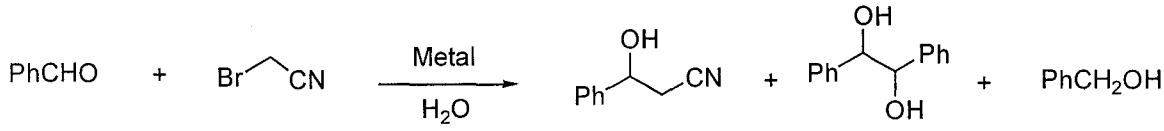
Additive	Yields
Me_3SiCl	86
$^tBuMe_2SiCl$	58
$TiCl_4$	64
SnCl4	34
$BF_3.OEt_2$	0
Me_3SiOTf	0

Scheme 5.11

All above reactions were performed in organic solvents and in particular, additives were generally required for the promotion of the reaction. As part of our effort to expand the scope of the aqueous Barbier-type reactions, we are interested in examining the possibility of such reaction in aqueous media.

In the screening of metals and conditions for this coupling reaction, the reaction of benzaldehyde and α-bromoacetonitrile was used as the model reaction. The results were summarized in Table 5.2. As one can see that in most cases, the pinnacol coupling products from the aldehyde and the alcohol from the reduction of the aldehyde were observed as the major products of the reaction. Among the metals, bismuth and indium only gave the reduction product from the aldehyde (*Table 5.2. entries 4, 5*), manganese activated by cupper(I) chloride gave the pinnacol coupling product (*entry 3*). When tin powder was employed, only trace amount of the expected product was observed. (*entries 1, 2*). More encouraging results were observed when zinc powder was used; the reaction gave 42% yield when promoted by sonication. However, under the benzylation reaction

conditions with silver salt, which we employed in the earlier part of this chapter, only the pinnacol coupling and reduction were observed (*entry 6*).



5.15 **5.16** **5.17** **5.18** **5.19**

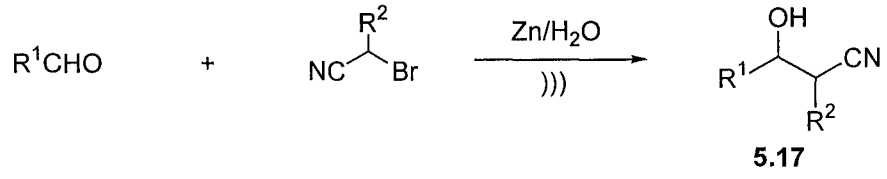
Table 5.2 Screening of Metals for the Coupling Reaction of Bromoacetonitrile with benzaldehyde

Entry	Reaction condition	Product[a] **5.15 : 5.17 : 5.18 : 5.19**	Yield% of **5.17**[b]
1	$Sn/H_2O/HBr$, 20hr.	20:1:0:0	5%
2	Sn/NH_4Cl))), 2hr	no reaction	----
3	$Mn/H_2O/CuCl$/6hr	1:trace:4:0	trace
4	$Bi/H_2O/Bu_4NF$	only **5.15, 5.19** was recovered	----
5	In/H_2O/10hr	only **5.15, 5.19** were recovered	----
6	$Zn/H_2O/AgNO_3/K_2PO_4$	**5.15, 5.18, 5.19** were recovered	----
7	Zn/H_2O)))/10hr	1:2.5:0:2	42[c]
8	Zn/NH_4Cl/6hr	1:2:7:2	15

[a] The ratio of the products is determined by ^1H NMR. [b] Yield determined by ^1H NMR.
[c] Isolated yield.

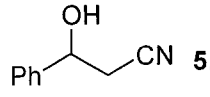
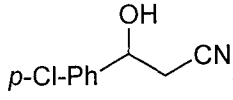
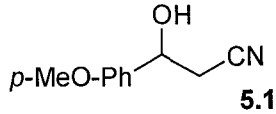
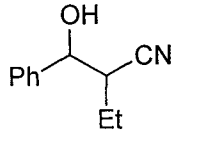
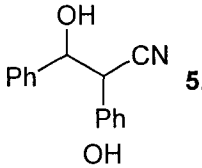
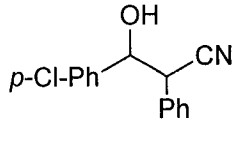
Under the optimized reaction conditions of zinc/H_2O/sonication, several α-bromoacetonitriles with a number of aldehydes were examined. It could be seen that various β-hydroxynitriles could be obtained in moderate yields (*Table 5.3, entries 1, 2, 4~6*). The electron-donating group on the substrate, which can reduce the electrophilicity of the aldehyde, led to the failure of the coupling reaction (*entry 3*). In most cases,

moderate yields could be obtained. In comparison with the reaction in organic solvents, the reaction condition is mild and no additive is necessary for the promotion of the reaction.



5.17

Table 5.3 Zinc-Mediated Coupling Reaction of Bromoaceonitrile with Aldehyde in Water

Entry	R^1	R^2	Product	yield%[a]
1	Ph	H	 **5.17a**	42
2	*p*-Cl-Ph	H	 **5.17b**	33
3	*p*-MeO-Ph	H	 **5.17c**	0
4	Ph	Et	 **5.17d**	46
5	Ph	Ph	 **5.17e**	38
6	*p*-Cl-Ph	Ph	 **5.17f**	39

[a] Isolated yields

Discussion: Mediated by zinc, the coupling reaction of bromoacetonitrile with aldehydes can be realized in water with moderate yields. Again, we still have little knowledge about

the mechanism of this coupling reaction. However, once again, zinc showed its greater reactivity than other metals like indium and tin in aqueous organometallic reactions. Our results suggest that the generated organoindium species from the corresponding bromoacetonitrile are not reactive enough for the further coupling with aldehydes. On the other hand, radical species may be involved in the zinc-mediated process and they are reactive enough for the further coupling with aldehydes, even without the promotion of Lewis acid. It is also a common observation in organic chemistry that radical species are usually more reactive than the corresponding carbanion in organic reactions.[17]

5.4 Conclusions

In our efforts to expand the scope of the aqueous Barbier-type reactions, the aqueous Barbier-type benzylation of sulfonimines and the coupling reaction of α-bromoacetonitriles with aldehydes were examined. Zinc was found to be the metal of choice for mediation of both reactions. In the benzylation reaction of sulfonimines catalyzed by silver salt, moderate to good yields were obtained. Moderate yields were obtained in the addition reaction of α-bromoacetonitriles with aldehydes in water under sonication. In comparison with similar coupling reactions in organic solvents, the reaction condition is milder and no additive was required for the reaction.

5.5 Experimental Section

General Section

See Chapter 2, Experimental Section.

General procedure of the aqueous Barbier-type benzylation reaction of sulfonimines mediated by zinc

K_2HPO_4 (3 g) and $AgNO_3$ (4 mg) were dissolved in water (3 mL) at room temperature. Sulfonimine (1 mmol) and benzyl chloride (1.5 mmol) were then added. Under vigorous stirring, zinc powder (4 mmol) was added. After 2hr of stirring, the reaction was quenched by adding of 1N HCl (2 mL). The reaction mixture was extracted by diethyl ether (2 × 20 mL). The combined organic layer was washed with sodium bicarbonate saturated aqueous solution and brine respectively. The product was obtained by evaporation of the solvent and further purified by flash column chromatography (eluent: hexane:ethyl acetate/10:1).

N-**(1,2-Diphenyl-ethyl)-benzenesulfonamide (5.10a)** IR(neat, cm^{-1}):2780.8, 1448.1, 1323, 1160.1; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45-7.38 (m, 2H), 7.25-7.15(m, 1H), 7.10-6.99 (m, 2H), 6.99-6.88 (m, 6H), 6.88-6.78 (m, 2H), 6.86-6.75 (m, 2H), 5.08 (d, 2H, J = 6.52 Hz), 4.31 (dt, 1H, J = 6.95, 6.95 Hz), 2.76 (d, 2H, J = 7.06 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.44, 140.38, 136.63, 132.43, 129.60, 128.99, 128.81, 128.63, 127.78, 127.28, 127.14, 127.03, 60.52, 45.43; MS (CI, NH_3) m/e: 338 ($M+H^+$, 3.8), 246 (100); HRMS Calcd for $C_{20}H_{19}NO_2S+H^+$ 338.1215, found 338.1215.

N-[1-(4-Methoxy-phenyl)-2-phenyl-ethyl]-benzenesulfonamide (5.10b) IR(neat, cm^{-1}): 1613.5, 1514.5, 1323.3, 1160.3; ^1H NMR (200 MHz, $CDCl_3$): δ 7.56-7.51 (m, 2H), 7.50-7.40 (m, 1H), 7.30-7.26 (m, 2H), 7.15-7.12 (m, 3H), 6.95-6.90 (m, 4H), 6.66-6.62 (m, 2H), 5.28 (d, 1H, J = 6.52 Hz), 4.46 (dt, 1H, J = 6.96, 6.96 Hz), 3.71 (s, 3H), 2.95 (d, 2H, J = 7.2 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 158.79, 140.42, 136.80, 132.62,

132.38, 129.60, 128.98, 128.21, 127.30, 127.07, 114.09, 60.05, 56.40, 45.39; MS (CI, NH_3) m/e: 368 ($M+H^+$, 0.2), 276 (100); HRMS Calcd for $C_{21}H_{21}NO_3S+H^+$ 368.1320, found 368.1322.

N-(2-Phenyl-1-p-tolyl-ethyl)-benzenesulfonamide (5.10c), IR(neat, cm^{-1}): 3279, 1447.7, 1321.0, 1159.5; ^1H NMR (200 MHz, $CDCl_3$): δ 7.58-7.54 (m, 2H), 7.45-7.40 (m, 1H), 7.32-7.24 (m, 2H), 7.18-7.15 (m, 3H), 6.95-6.92 (m, 6H), 5.28 (br, 1H), 4.46 (dt, 1H, J = 6.96, 6.96 Hz), 2.98 (d, 2H, J = 7.18 Hz), 2.27 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.35, 137.58, 137.29, 136.82, 132.33, 129.60, 129.31, 128.96, 128.79, 127.31, 127.07, 126.95, 60.33, 45.37, 22.63; MS (CI, NH_3) m/e: 369 ($M+H_2O$, 2.4), 260 (100); HRMS Calcd for $C_{21}H_{21}NO_2S+H^+$ 352.1371, found 352.1372.

N-[1-(4-Chloro-phenyl)-2-phenyl-ethyl]-benzenesulfonamide (5.10d) IR(neat, cm^{-1}): 2888.0. 1447.6, 1321.3, 1159.5; ^1H NMR (200 MHz, $CDCl_3$): δ 7.65-6.85 (m, 14H), 5.25 (d, 1H, J = 6.22 Hz), 4.51 (dt, 1H, J = 6.83, 6.83 Hz), 2.94 (d, 2H, J = 7.32 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.06, 139.02, 136.06, 133.50, 132.60, 129.50, 129.07, 128.97, 128.75, 128.44, 127.36, 127.27, 59.79, 45.22; MS (CI, NH_3) m/e: 389 ($M+H_2O$, 9.6), 260 (100); HRMS Calcd for $C_{20}H_{18}NO_2SCl+H^+$ 372.0825, found 372.0825.

N-[1-(2-Methoxy-phenyl)-2-phenyl-ethyl]-benzenesulfonamide (5.10e) IR(neat, cm^{-1}): 1601.8, 1493.8, 1446.6, 1323.6, 1161.1; ^1H NMR (200 MHz, $CDCl_3$): δ 7.55-7.48 (m, 2H), 7.36-7.26 (m, 1H), 7.24-7.07 (m, 5H), 7.07-6.95 (m, 1H), 6.96-6.88 (m, 2H), 6.72-6.58 (m, 3H), 5.74 (d, 1H, J = 9.46 Hz), 4.46 (dt, 1H, J = 9.40, 7.26 Hz), 3.69 (s, 3H), 3.05 (d, 2H, J = 7.34 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 156.24, 140.57, 137.70, 132.13, 129.62, 129.42, 128.90, 128.67, 128.48, 127.50, 127.07, 126.74, 120.75, 111.01,

59.61, 56.29, 43.55; MS (CI, NH_3) m/e: 368 ($M+H^+$, 1.3), 276 (100); HRMS Calcd for $C_{21}H_{21}NO_3S+H^+$ 368.1320, found 368.1322.

N-(1-Benzyl-2-methyl-but-2-enyl)-benzenesulfonamide (5.10f) IR(neat, cm^{-1}): 3278.0, 2917.9, 1447.6, 1325.1, 1160.2; ^1H NMR (200 MHz, $CDCl_3$): δ 7.75-7.65 (m, 2H), 7.60-7.40 (m, 3H), 7.30-7.15 (m, 3H), 7.10-6.95 (m, 2H), 5.24-5.15 (m, 1H), 4.81 (d, 1H, J = 6.28 Hz), 3.92 (dt, 1H, J = 6.92, 6.92 Hz), 2.75 (d, 2H, J = 7.2 Hz), 1.37 (d, 3H, J = 5.86 Hz), 1.36 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 140.57, 137.16, 133.15, 132.4, 129.34, 128.86, 128.79, 127.58, 127.40, 127.00, 123.81, 63.70, 41.71, 14.69, 13.06; MS (CI, NH_3) m/e: 316 ($M+H^+$, 14.8), 224 (100); HRMS Calcd for $C_{18}H_{21}NO_2S+H^+$ 316.1372, found 316.1374.

N-[1-(4-Isopropenyl-cyclohex-1-enyl)-2-phenyl-ethyl]-benzenesulfonamide (5.10g) IR(neat, cm^{-1}): 3273.8, 1447.4, 1322.5, 1160.6; ^1H NMR (200 MHz, $CDCl_3$): δ 7.76-7.71 (m, 2H), 7.52-7.37 (m, 3H), 7.26-7.19 (m, 3H), 7.18-7.01 (m, 2H), 5.42-5.30 (br, 1H), 5.09 (t, 1H, J = 8.04 Hz), 4.65-4.56 (m, 2H), 4.05-3.92 (m, 1H), 2.77 (d, 2H, J = 7.32 Hz), 2.05-1.52 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 149.61, 140.97, 137.16, 134.67, 132.47, 129.47, 128.97, 128.72, 127.68, 127.46, 126.95, 109.19, 62.22, 42.23, 41.68, 31.78, 28.43, 25.64, 22.32; MS (CI, NH_3) m/e: 382 ($M+H^+$, 4.4), 290 (100); HRMS Calcd for $C_{23}H_{27}NO_2S+H^+$ 382.1841, found 382.1841.

N-[2-(4-Methoxy-phenyl)-1-phenyl-ethyl]-benzenesulfonamide (5.10h) IR(neat, cm^{-1}): 3279.5, 1612.7, 1513.3, 1322.3, 1247.7, 1159.6; ^1H NMR (200 MHz, $CDCl_3$): δ 7.55-7.50 (m, 2H), 7.44-7.36 (m, 1H), 7.30-7.21 (m, 2H), 7.15-7.10 (m, 3H), 7.06-6.99(m, 2H), 6.80 (d, 2H, J = 8.66 Hz), 6.66 (d, 2H, J = 8.6 Hz), 5.15 (d, 1H, J = 6.3 Hz), 4.47 (dt, 1H, J = 6.84, 6.84 Hz), 3.74 (s, 3H), 2.90 (dd, 1H, J = 7.68, 2.2 Hz); ^{13}C NMR (50.3

MHz, $CDCl_3$): δ 158.40, 140.51, 140.30, 132.41, 130.56, 128.95, 128.61, 128.52, 127.74, 127.29, 127.02, 114.41, 60.50, 56.37, 44.55; MS (CI, NH_3) m/e: 385 (M^++H_2O, 1.72), 246 (100); HRMS Calcd for $C_{21}H_{21}NO_3S$+H^+ 368.1320, found 368.1322.

N-[2-(4-Methyl-phenyl)-1-phenyl-ethyl]-benzenesulfonamide (5.10i) IR(neat, cm^{-1}): 3272.1, 1558.2, 1518.5, 1456.1, 1321.4, 1159.2; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54-6.80 (m, 14H), 4.91 (d, 1H, J = 6.0 Hz), 4.47 (dt, 1H, J = 6.80, 6.80 Hz), 2.94 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.59, 140.30, 136.71, 133.26, 132.37, 129.53, 129.36, 128.87, 128.57, 127.71, 127.24, 126.94, 59.44 43.91, 21.28; MS (CI, NH_3) m/e: 352 (M+H^+, 1.40), 246 (100); HRMS Calcd for $C_{21}H_{21}NO_2S$+H^+ 352.1371, found 352.1374.

N-[2-(4-Chloro-phenyl)-1-phenyl-ethyl]-benzenesulfonamide (5.10j) IR(neat, cm^{-1}): 3276.5, 1492.7, 1447.2, 1321.9, 1159, 1093; ^1H NMR (200 MHz, $CDCl_3$): δ 7.54-6.80 (m, 14H), 5.38 (d, 1H, J = 7.26 Hz), 4.48(dt, 1H, J = 7.04, 7.04 Hz), 2.94 (d, 2H, J = 7.34 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.28, 140.15, 135.22, 132.48, 130.88, 129.43, 129.01, 128.84, 128.76, 127.94, 127.17, 126.90, 60.49, 48.55; MS (CI, NH_3) m/e: 372 (M^++H, 0.1), 246 (100); HRMS Calcd for $C_{20}H_{18}NO_2SCl$+H^+ 372.0825, found 372.0825.

General procedure of aqueous coupling reaction of α-bromoacetonitrile with aldehyde mediated by zinc:

To a round bottom flask was added aldehyde (1 mmol), α-bromoacetonitrile (2 mmol), zinc powder (4 mmol) and water (3 mL). Then 5 drops of saturated NH_4Cl aqueous solution was added. The mixture was vigorously shaked to ensure that the zinc powder

was evenly dispersed. Then the mixture was put under sonication for 20 h and was quenched by adding 1N HCl (2 mL). The reaction mixture was extracted with diethyl ether (2 × 20 mL) and the combined organic layer was washed with $NaHCO_3$ saturated aqueous solution and brine respectively. The pure product was obtained by flash column chromatography (10% ethyl acetate in hexane).

3-Hydroxy-3-phenypropanenitril (5.17a) [14] colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.03 (t, 1H, J = 6.0 Hz), 2.72 (d, 2H, J = 5.8 Hz), 2.5 (br, 1H).

3-Hydroxy-3-(4-chlorohenyl)propanenitril (5.17b)[14] colorless oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25-7.18 (m, 4H), 5.10 (t, 1H, J = 6.0 Hz), 2.70(d, 2H, J = 6.0 Hz), 2.38(br, 1H).

2-(Hydroxy-phenyl-methyl)-butyronitrile (5.17d)[18] colorless oil, syn: anti/1:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 4.75 (d, 1H, J = 6.5 Hz), 3.35 (br, 1H), 2.76-2.66 (m, 1H), 1.42-1.66 (m, 2H), 1.05 (t, 3H, J = 7.2 Hz)

3-Hydroxy-2,3-diphenyl-propionitrile (5.17e)[19] white solid, *syn: anti*/1:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-7.20 (m, 5H), 4.92 (dd, 1H, J = 3.5, 6.0 Hz), 4.02 (d, 1H, J = 5.9 Hz), 2.50 (d, 1H, J = 3.4 Hz)

3-(4-Chloro-phenyl)-3-hydroxy-2-phenyl-propionitrile (5.17f)[20] white solide, *syn: anti*/1:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-7.35 (m, 4H), 4.98 (dd, 1H, J = 3.8, 6.2 Hz), 4.02 (d, 1H, J = 6.1 Hz), 2.56 (d, 1H, J = 3.4 Hz)

5.6 References and Notes

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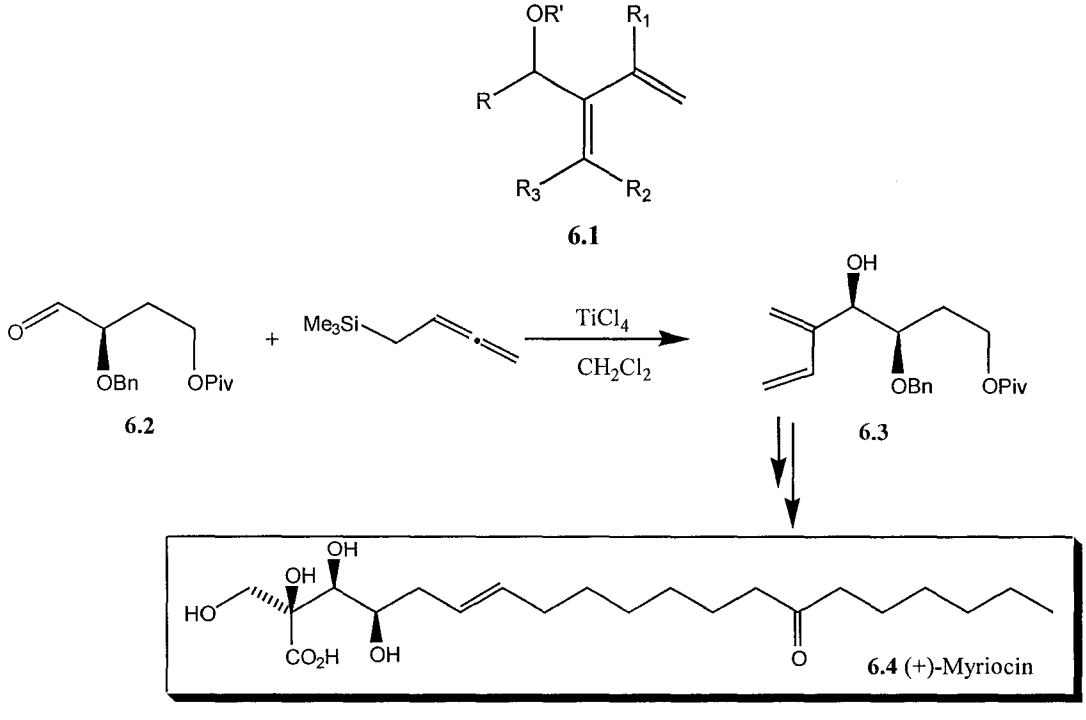
Chapter 6

Indium-Mediated 1,3-Butadien-2-ylation of Carbonyl Compounds. A Demonstration of Synthetic Application of Indium Chemistry in Aqueous Media

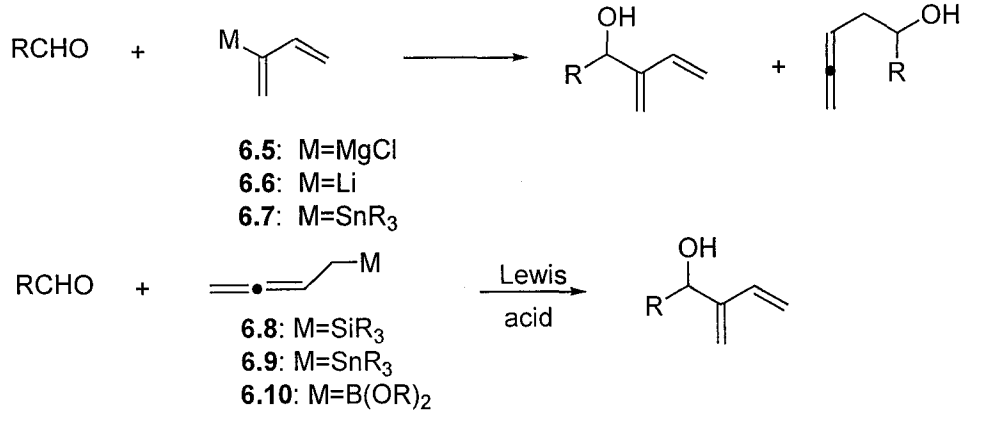
6.1 Introduction

Functionalized dienes are important building blocks in organic synthesis. Among them, dienols of general structure like **6.1** are valuable precursors for the synthesis of a variety of complex natural products.[1] One recent example is the total synthesis of (+)-Myriocin (**6.4**). Dienols **6.3** was synthesized as an key intermediate by the reaction of 1-trimethylsilybuta-2,3-diene with aldehyde **6.2**.[2] (Scheme 6.1)



Scheme 6.1

A number of reagents have been developed for the 1,3-butadien-2-ylation of carbonyl compounds (Scheme 6.2). Of these, 2-(1,3-butadienyl)magnesium chloride (**6.5**) suffers from poor regioselectivity.[3] The corresponding lithium compound **6.6** has to be prepared indirectly from the 2-stannyl compound **6.7**.[4]

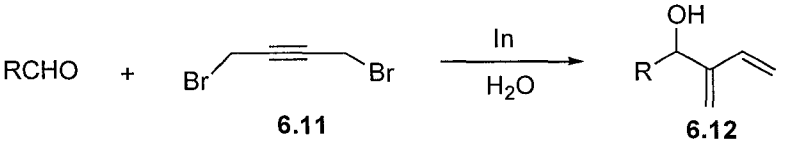


Scheme 6.2

The homoallenylic silane **6.8**,[5] stannane **6.9**[6] and boronate **6.10**,[7] though quite effective in reacting with carbonyl compounds to give regioselectively the 1,3-butadien-2-ylmethanols, are not convenient to prepare. From the viewpoint of atom economy,[8] all or theses reagents, requiring the use of silyl, stannyl or boron appendage, cannot be considered as atom economical.[9] Moreover, all the methodologies developed have to be carried out in organic solvents under strictly anhydrous conditions. It is therefore an interesting challenge to develop a mild and adaptable organometallic reagent for such reactions.

6.2. Indium-Mediated 1,3-Butadien-2-ylation of Carbonyl Compounds in Aqueous Media

The discovery[10] in the past decade that the allylation of carbonyl compounds could be achieved in aqueous media through a Barbier type reaction[11] has drawn much interest. Metals such as Zn[12], In[13], Bi[14], Sn[15], Pb[16], Mn[17], Mg[18], or Sb[19], have been reported to be effectively in mediating the coupling between allyl halides and carbonyl compounds to give the corresponding homoallylic alcohols in aqueous media. Among these reported metals, indium appears to be the metal of choice because it requires no activation, causes few side reactions, and is quite regio- and stereoselective.[20] The indium-mediated coupling reaction has been extended to propargylation of aldehydes.[21] We observed that the regioselectivity of this reaction was strongly influenced by the substituents on the propargyl bromides. When the propargyl bromides were γ-substituted with bulky group, propargylindium species was preferred as the reaction intermedate and gave allenic products predominately. Here, we furthered our study by using poly-functionalized propargylic bromide. We found that indium can effective mediate the coupling between 1,4-dibromobut-2-yne (**6.11**) and carbonyl compounds in aqueous media to give regioselectively the 1,3-butadien-2-ylmethanols **6.12** in good yields (Scheme 6.3).[22]



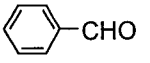
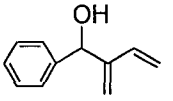
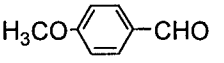
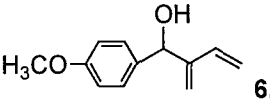
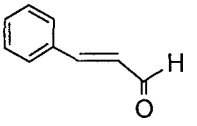
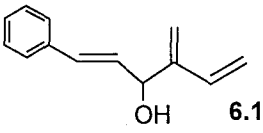
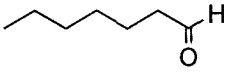
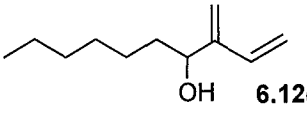
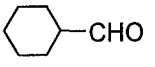
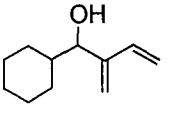
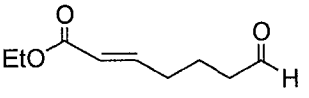
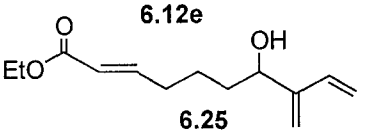
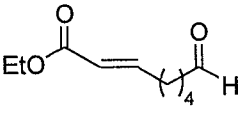
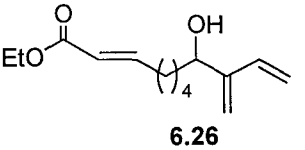
6.11 **6.12**

Scheme 6.3

The results are summarized in Table 6.1. As one can see, the reaction worked equally well for aryl and aliphatic aldehydes with good yields. With cinnamaldehyde

(*entry 3*), the coupling occurred selectively in a 1,2-addition fashion. Ester function is not affected (*entries 6-7*). Thus, indium-mediated aqueous 1,3-butadien-2-ylation of carbonyl compounds provides a mild approach for the synthesis of dienols with high regioselectivity.

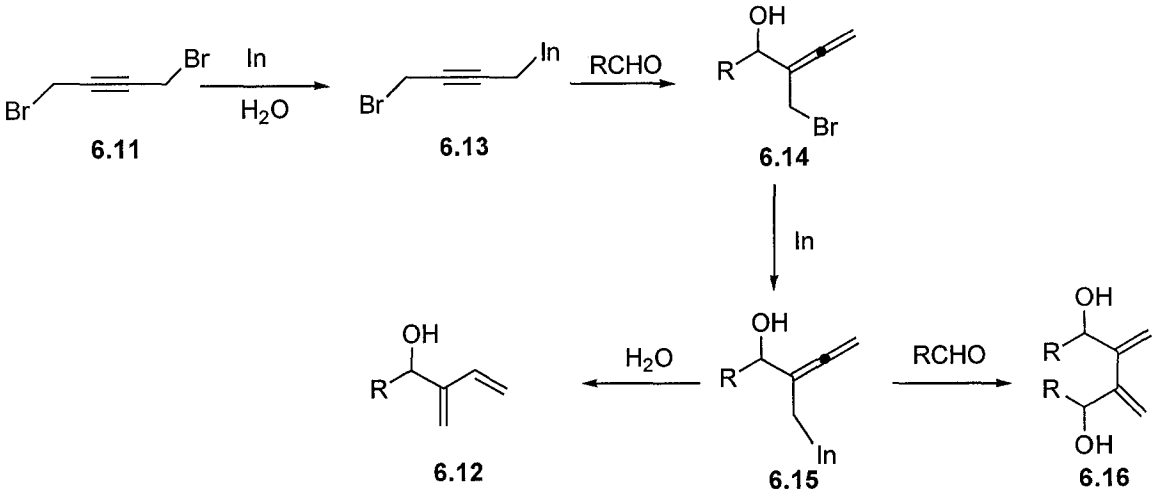
Table 6.1 Indium Mediated 1,3-Butadien-2-ylation of Carbonyl Compounds in Water

Entry	Aldehyde	Product	Yield %[a]
1		 **6.12a**	53
2		 **6.12b**	55
3		 **6.12c**	60
4		 **6.12d**	64
5		 **6.12e**	67
6	 **6.24a**	 **6.25**	68
7	 **6.24b**	 **6.26**	65

[a] Isolated yield.

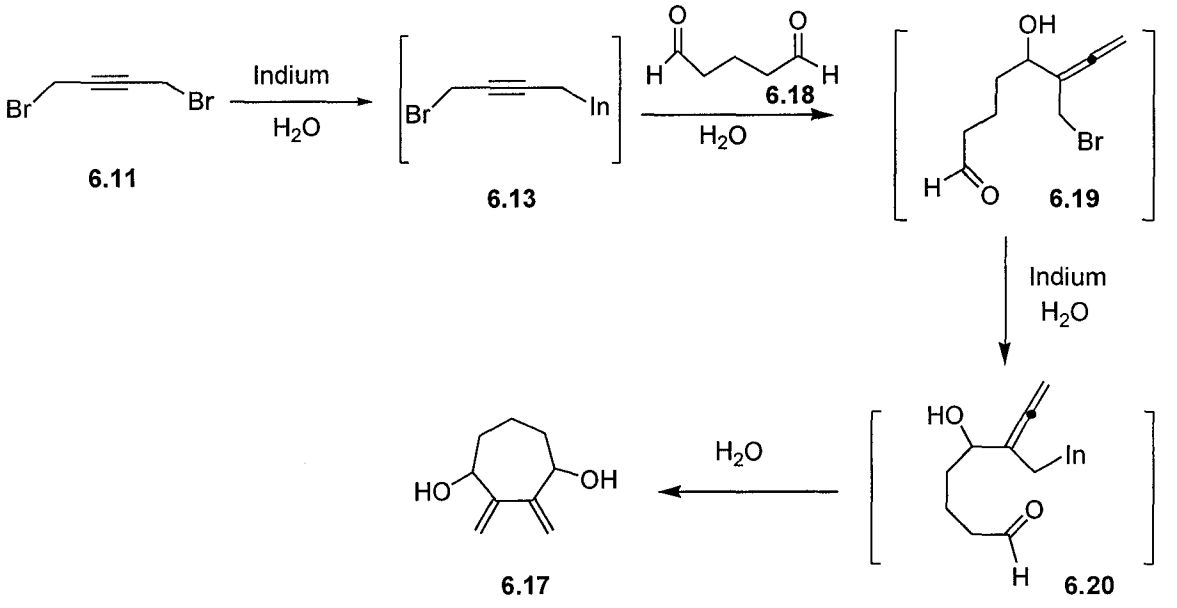
As far as the mechanism is concerned, the first step should involve the generation of an organoindium species **6.13** *in situ* by the reaction of 1,4-dibromobut-3-yne **6.11** with indium. The reaction of the organoindium species **6.13** with aldehyde gives adduct **6.14**.

Further reaction of the bromide with indium can lead to another organoindium intermediate **6.15** which is quenched by water to give 1, 3-butadienyl-2-methanol **6.12**.



Scheme 6.4

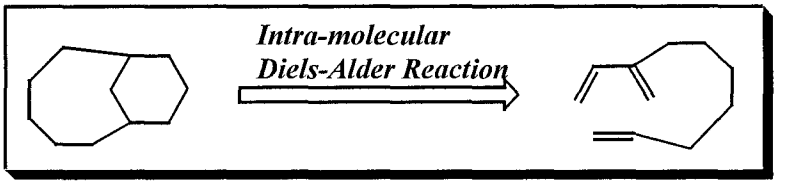
Reaction of **6.15** with another molecule of aldehyde to give the di-adduct **6.16** was not observed, presumably because of steric hindrance. However, we were able to show that with glutaric dialdehyde **6.18**, intramolecular trapping of the intermediate **6.20** was possible, and the cyclic di-adduct **6.17** was obtained in 40% isolated yield (Scheme 6.5). This result not only verified the process of aqueous indium-mediated 1,3-butadien-2-ylation of aldehyde in this reaction, it also provided a novel facile way to the synthesis of functionalized seven-member ring compounds in aqueous media.

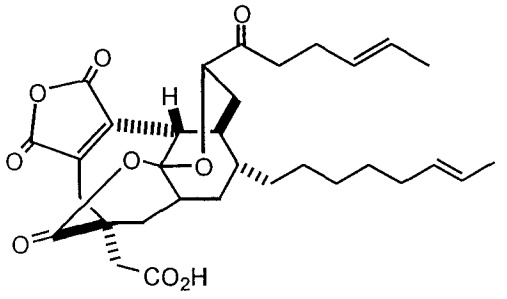


Scheme 6.5

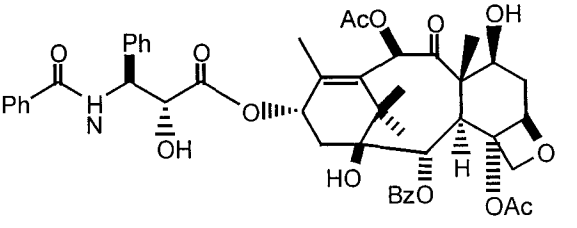
6.3. Intramolecular Diels-Alder Reaction: The Potential of Aqueous Indium Chemistry in the Synthesis of Taxoid Skeleton

Intramolecular Diels-Alder reaction (IMDA) is an important strategy to synthesize fused ring system, which has been found widely in natural products. For example, IMDA reaction has been used as the key step in the synthesis of the (8, 6)-fused ring skeletons of (-)CP-263,114[23] and taxol.[24] (Scheme 6.6)





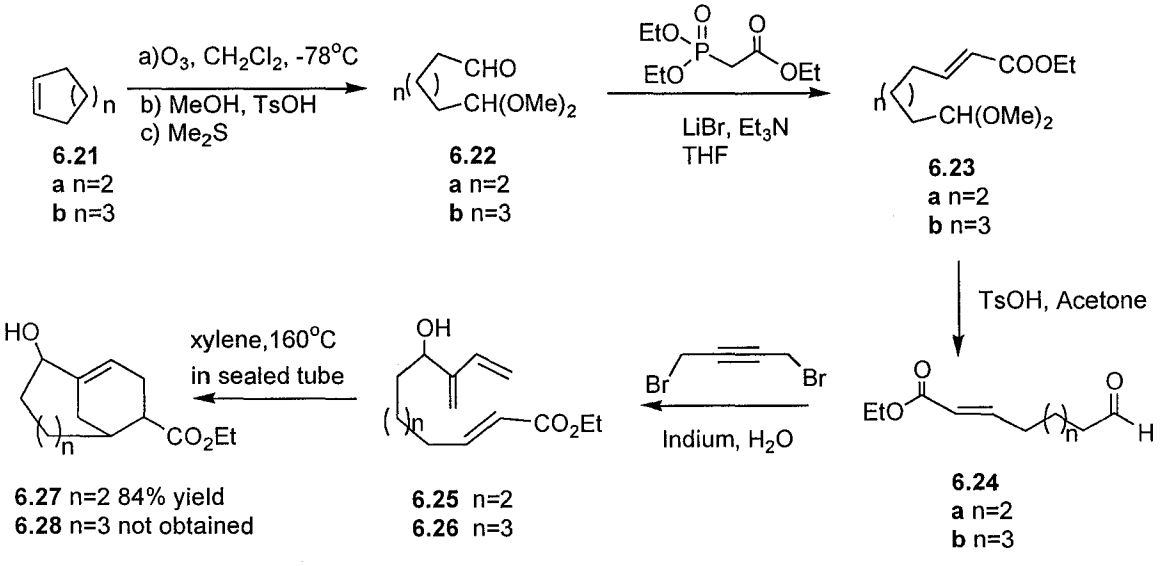
CP-263,114



Taxol

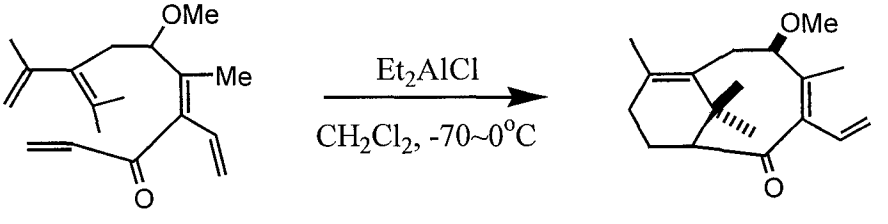
Scheme 6.6

The aqueous strategy to prepare dienols provides us a facile way to synthesize the corresponding precursor for such IMDA reaction. To initiate our study, it was first of all necessary to synthesize the properly functionalized aldehyde. Cycloalkene (**6.21a** n=1, **6.21b** n=2) was subjected to ozonolysis and one end of the aldehyde was protected by dimethyl acetal in a one pot process. The Horner-Wadsworth-Emmons reaction of **6.22** led to the α,β-unsatuated ester **6.23**, which, on deprotection of the dimethyl acetal function, offered the desired aldehyde **6.24**. The reaction of **6.24** with 1,4-dibromobut-2-yne and indium in water gave compounds **6.25** or **6.26** in good yields (Table 6.1, entries 6 and 7), which could serve as the precursors for IMDA reaction studies.[25] (Scheme 6.7)



Scheme 6.7

The IMDA reaction was realized when compound **6.25** was heated in xylene at 160 °C in a sealed tube for 8 hrs, the adduct **6.27** was obtained in 84 % yield. However, under similar conditions, the attempt to construct the (8, 6)-fused ring compound **6.28** by IMDA reaction from dienol **6.26** was unsuccessful. Decomposition or polymerization was found under the reaction conditions. The failure of these attempts might be due to the sensitivity to heat of the substrate.

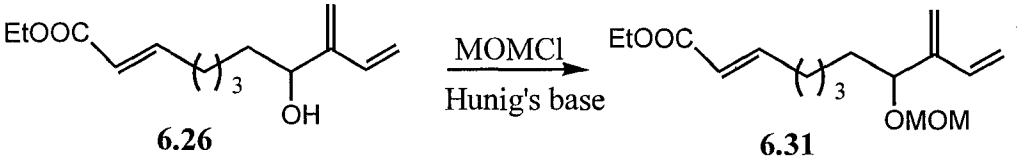


6.29 **6.30**

Scheme 6.8

Quite recently, Fallis *et al* reported that the diene **6.29,** when catalyzed by Lewis acid Et_2AlCl, could gave the IMDA adduct **6.30**.[26] (Scheme 6.8) We believe that by choosing a suitable catalyst, it is still possible to realize the IMDA reaction under relative

mild conditions. We started our investigation by trying three kinds of Lewis acids as the common catalysts for IMDA reaction. (Scheme 6.9) The hydroxyl function on the dienol **6.26** was first protected with MOM, then **6.31** was subjected to the Lewis acids as well as to high temperature in a sealed tube as shown in Scheme 6.9. Unfortunately, none of the reactions gave the desired product. Despite the similarity between **6.31** and **6.29**, the skeleton of **6.31** is still too flexible to favor the geometry requirement of the IMDA reactions. Further modification of the skeleton of this precursor is apparently necessary.



6.26 **6.31**

6.31 $\xrightarrow[\text{DCM, -20 °C}]{BF_3.OEt}$ decomposed or polymerized

6.31 $\xrightarrow[\text{DCM, -20 °C~rt}]{Me_2AlCl}$ no reaction, SM recovered

6.31 $\xrightarrow[\text{DCM, -20°C~rt}]{Et_2AlCl}$ no reaction, SM recovered after over night

6.31 $\xrightarrow[\text{150 °C, 1hr.}]{\text{Toluene}}$ decomposed, trace recovered SM

Scheme 6.9

6.4 Conclusion

Indium-mediated aqueous Barbier-type reaction of 1,4-dibromo-but-2-yne with aldehydes was studied. The reaction was found to provide a facile synthesis of 2-substituted 1,3-butadienes. The further IMDA reaction of the properly functionalized 1,3-dienols can provide a potential strategy for the taxoid skeleton synthesis. The

mechanism of the reaction was briefly examined. In view of the simplicity of the present process for the synthesis of 2-substituted 1,3-butadienes in aqueous media, the reaction is likely to find considerable applications in synthesis.

6.5 Experimental Section

6.5.1 General Aspect. See Chapter 2, Experimental Section.

6.5.2 1,4-Dibromobut-2-yne (6.11)

To a 100 mL round-bottom flask with but-2-yne-1,4-diol (5 g, 58 mmol) and dichloromethane (50 mL), was added PBr_3 (16g, 59 mmol) dropwise via a dripping funnel. The reaction was stirred over night at room temperature and was quenched by pouring into iced water (100 mL). The two phases were separated, and the aqueous phase was extracted with dichloromethane (2 X 15 mL). The combined organic layers were washed with $NaHCO_3$ saturated solution and brine respectively and dried with Na_2SO_4. Pure 1,4-dibromobut-2-yne (**6.11**) was obtained as colorless liquid by evaporation of the solvent and vacuum distillation (74~78 ^oC/2 mmHg).

6.5.3 General procedure for the synthesis of aldehyde 6.24

a. Ozonolysis of cycloalkene (6.21):

The cycloalkene (10 mmol) was dissolved in dichloromethane (100 mL) and the solution was cooled to –78^oC. Ozone was bubbled through the solution via an ozone generator at a speed of 0.007 mol/h until a light blue persistent color as an indication of excess ozone was seen in the solution. The ozone generator was switched off and

oxygen was bubbled through the solution to expel the excess ozone until the disappearance of the blue color. Methanol (40 mL) and *p*-toluenesulfonic acid (0.1 mmol) were added. The solution was stirred at room temperature for 4h. Then dimethyl disulfide (5 mL) was added, and the solution was stirred over night. The desired product **6.22** was obtained by filtration of the solution via silica gel (5g) and evaporation of the solvent, and was used directly for the next step.

b. The Horner-Wadsworth-Emmons reaction

Anhydrous LiBr (12 mmol) was dissolved in anhydrous THF (100 mL), and the solution was treated with triethylamine (12 mmol) and (diethoxy-phosphoryl)-acetic acid ethyl ester (10 mmol) respectively under argon at 0 °C. The aldehyde **6.22** obtained above was added via a syringe. The solution was stirred at room temperature over night. The reaction mixture was filtered through silica gel and washed with diethyl ether. The crude **6.23** was obtained by evaporation of organic solvent and used directly for the next step.

c. Deprotection of dimethyl acetal:

To a solution of **6.23** in acetone (50 ml), *p*-toluenesulfonic acid (0.1 mmol) was added. The mixture was stirred at room temperature and monitored by TLC. Upon disappearance of **6.23**, the reaction was quenched by neutralization of the acid with $NaHCO_3$ and diethyl ether (150 mL) was added. The organic layer was washed with brine twice and dried with Na_2SO_4. The crude product **6.24** was obtained by evaporation of the organic solvent and purified by silica gel flash chromatography with hexane and ethyl acetate as eluent.

7-oxo-hept-2-enoic acid ethyl ester (6.24a): ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 9.77 (t, 1H, J = 1.8 Hz), 6.98-6.88 (m, 1H), 5.82 (dt, 1H, J = 15.6, 1.8 Hz), 4.17 (q, 2H, J = 7.2 Hz), 2.46 (dt, 2H, J = 7.5, 1.8 Hz), 2.23 (dt, 2H, J = 7.2, 1.8 Hz), 1.75-1.42 (m, 2H), 1.28 (t, 3H, J = 7.2 Hz).

6.5.4 Standard procedure for the reaction of aldehydes with 6.11

To a mixture of aldehyde (1 mmol) in water (5 mL) and the bromide **6.11** (1.5 mmol), indium powder (3 mmol) was added in one portion and the mixture was vigorously stirred for 6 h. Ethyl ether was added and the organic layer was separated. The aqueous phase was extracted with ethyl ether. The organic extracts were combined, dried over Na_2SO_4, and was filtered and evaporated. The residue afforded the corresponding 1,3-butadien-2-ylmethanols **6.12** as the major product according to ^{1}H NMR. If necessary, purification was performed by flash chromatography over silica gel using hexane and ethyl acetate as eluent.

6.5.5 Procedure for IMDA reaction.

In a sealed tube, compound **6.25** (45 mg, 0.2 mmol) was dissolved in xylene (5 mmol). The reaction mixture was heated at 160 °C for 8 h and monitored by TLC. Upon the disappearance of **6.25**, the IMDA product **6.27** was obtained with 84% yield by evaporation of xylene under vacuo, and purified by flash column chromatography with hexane and ethyl acetate as eluent.

2-Methylene-1-phenyl-but-3-en-1-ol (6.12a)[27]: ^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 7.42-7.13 (m, 5H), 6.32 (dd, 1H, *J* = 17.7, 11.1 Hz), 5.47 (s, 1H), 5.42 (s, 1H), 5.23 (d, 1H, *J* = 17.7 Hz), 5.05 (d, 1H, *J* = 11.1 Hz), 2.15 (br. 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 147.82, 142.20, 136.08, 128.76, 128.10, 127.17, 116.01, 115.74, 74.21.

1-(4-Methoxy-phenyl)-2-methylene-but-3-en-1-ol (6.12b)[28]: ^{1}H NMR (300MHz, $CDCl_3$): 7.30 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 6.31 (dd, 1H, *J* = 17.6, 11.2 Hz), 5.43 (d, 1H, *J* = 10 Hz), 5.34 (s, 1H), 5.17 (d, 1H, *J* = 17.6 Hz), 5.02 (d, 1H, *J* = 10.8 Hz), 3.78 (s, 3H), 2.03 (br, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 159.48, 147.86, 136.22, 134.41, 138.52, 115.66, 115.58, 114.12, 73.61, 55.50.

4-Methylene-1-phenyl-hexa-1,5-dien-3-ol (6.12c)[27]: colorless oil, ^{1}H NMR (300MHz, $CDCl_3$): 7.22-7.10 (m, 5H), 6.67 (d, 1H, *J* = 15.9 Hz), 6.38 (dd, 1H, *J* = 18, 11.1 Hz), 6.31 (dd, 1H, *J* = 15.9, 6 Hz), 5.44 (d, 1H, *J* = 18 Hz), 5.38 (s, 1H), 5.26 (s, 1H), 5.16 (d, 1H, *J* = 11.1 Hz), 5.09 (br, 1H), 1.91 (d, 1H, *J* = 3.3 Hz); ^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 147.61, 136.82, 136.09, 131.49, 130.51, 128.82, 128.02, 126.82, 115.56, 115.46, 72.47.

3-Methylene-dec-1-en-4-ol (6.12d)[28]: colorless oil, ^{1}H NMR (300MHz, $CDCl_3$): 6.32 (dd, 1H, *J* = 17.7, 11.1 Hz), 5.31 (d, 1H, *J* = 17.7 Hz), 5.20 (d, 1H, *J* = 1.5 Hz), 5.14 (s, 1H), 5.08 (d, 1H, *J* = 11.1 Hz), 4.40 (dt, 1H, *J* = 6.9, 4.4 Hz), 1.68-1.20 (m, 9H), 0.90-0.80 (m, 5H); ^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 149.51, 136.46, 114.52, 114.17, 71.85, 36.62, 32.05, 29.45, 26.01, 22.86, 14.34.

1-Cyclohexyl-2-methylene-but-3-en-1-ol (6.12e)[27]: colorless oil, ^{1}H NMR (300MHz, $CDCl_3$): 6.31(dd, 1H, J = 17.6, 10.8 Hz), 5.36 (d, 1H, J = 17.6Hz), 5.19 (s, 1H), 5.13 (s, 1H), 5.09 (d, 1H, J = 11.2 Hz), 4.11 (d, 1H, J = 6 Hz), 1.86-1.81(m, 1H), 1.81-1.45 (m, 7H), 1.2-0.96 (m, 6H); ^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 148.24, 136.40, 114.96, 114.80, 77.10, 42.05, 30.18, 27.96, 26.68, 26.57, 26.31.

7-Hydroxy-8-methylene-deca-2,9-dienoic acid ethyl ester (6.25): colorless oil, ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 6.98-6.91, (m, 1H), 6.32 (dd, 1H, J = 17.6, 10.8Hz), 5.83-5.78 (dt, 1H, J = 15.2, 1.2 Hz), 5.32 (d, 1H, J = 17.6 Hz), 5.22 (d, 1H, J = 1.2 Hz), 5.15 (s, 1H), 5.09 (d, 1H, J = 11.6 Hz), 4.44-4.39 (br., 1H), 4.17 (q, 2H, J = 7.6 Hz), 2.28-2.18 (m, 2H), 1.75-1.48 (m, 5H), 1.27 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 116.94, 149.19, 149.12, 136.28, 121.75, 114.67, 114.35, 71.48, 60.40, 35.81, 32.24, 24.35, 14.49.

8-Hydroxy-9-methylene-undeca-2,10-dienoic acid ethyl ester (6.26): colorless oil, ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 6.94 (ddd, 1H, J = 16, 14, 6.8 Hz), 6.32 (dd, 1H, J = 18, 11.6 Hz), 5.79 (dt, 1H, J = 15.6, 1.6 Hz), 5.31(d, 1H, J = 17.6 Hz), 5.21(d, 1H, J = 0.4 Hz), 5.14 (s, 1H), 5.09 (d, 1H, J = 11.2 Hz), 4.40 (dt, 1H, J = 4.4, 4.4 Hz), 4.16 (q, 2H, J = 7.0 Hz), 2.24-2.16 (m, 2H), 1.73-1.64 (m, 2H), 1.61-1.34 (m, 5H), 1.25 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 167.0, 149.37, 149.37, 136.36, 121.61, 114.57, 114.27, 71.62, 60.39, 36.23, 32.37, 28.14, 25.54, 14.50.

2-Hydroxy-bicyclo[4.3.1]dec-1(9)-ene-7-carboxylic acid ethyl ester (**6.27**): colorless oil, ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 5.76(m, 1H), 4.24(t, 1H, J = 8.0 Hz), 4.13 (q, 2H, J = 6.8 Hz), 2.51 (br., 1H), 2.39-2.32 (m, 1H), 2.27 (d, 1H, J = 13.2 Hz), 2.22-2.15 (m, 1H), 2.13-2.05 (m, 1H), 1.94-1.86 (m, 2H), 1.58-1.52 (m, 1H), 1.49-1.38 (m, 2H) 1.34-1.28 (m, 2H), 1.24 (t, 3H, J = 7.2 Hz), 1.00-0.89 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 176.60, 143.95, 126.0, 74.84, 60.63, 47.10, 38.43, 36.10, 35.24, 27.46, 27.22, 21.36, 14.50; IR (neat on NaCl, cm^{-1}), 2928.4, 1730.2, 1446.4, 1373.7, 1267.2, 1189.2; MS (FAB): 224 (M, 8.8), 207 (48), 133 (100); HRMS (FAB): calcd. for $C_{13}H_{20}O_3 + H^+$ 225.1490, found 225.1491.

2,3-Dimethylene-cycloheptane-1,4-diol (**6.17**) white solid, mp: 67-69 °C, IR (neat on NaCl, cm^{-1}), 3370.3, 2929.9, 1626.4, 1447, 1011.6, 905.7; ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) 5.19-5.18 (m, 2H), 5.15-5.14(m, 2H), 5.48-5.46 (m, 2H), 1.82-1.64 (m, 8H); ^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 152.38, 113.34, 73.82, 37.10, 19.85; MS (EI), 154 (M^+, 0.8), 136 (68), 108 (100), HRMS (EI): calcd. for $C_9H_{14}O_2$-H_2O 136.0888, found 136.0886.

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Chapter 7

Conclusions and Future Perspectives

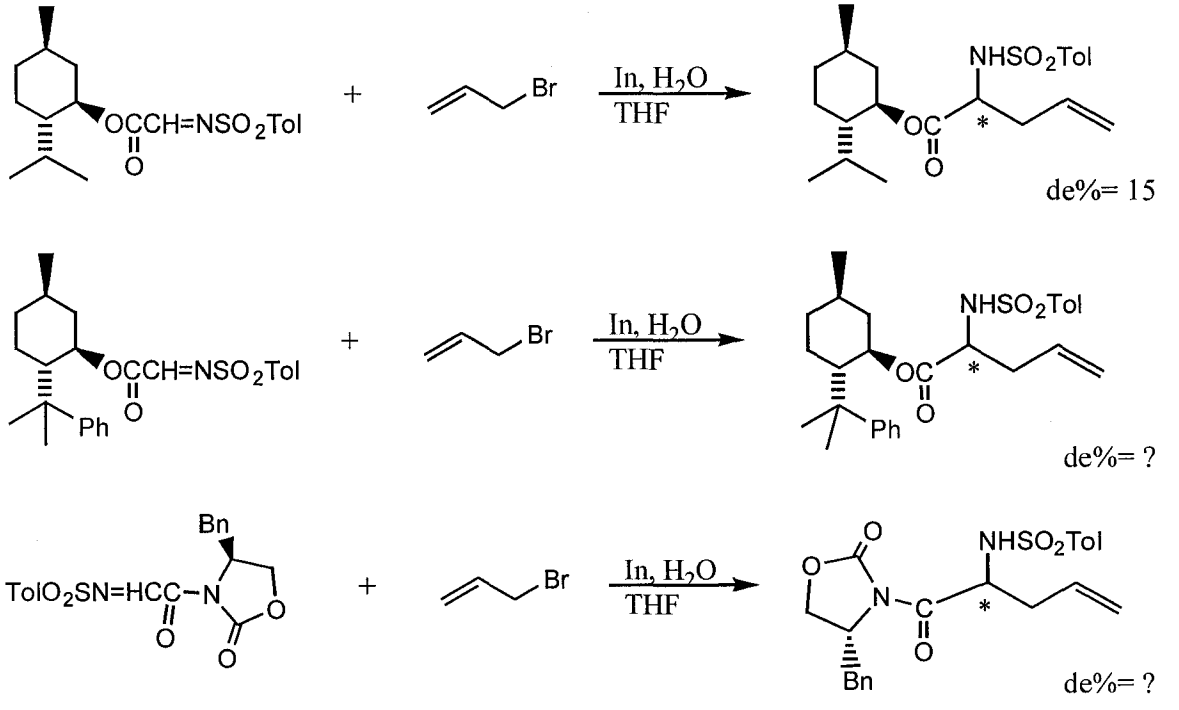
7.1. Introduction

With more than ten years' exploration in our lab and others, we have experienced an inspiring journey on the chemistry of organometallic reactions in aqueous media.[1] For the scope expansion and stereoselectivity enhancement of this chemistry, our endeavor included the search for new electrophiles such as sulfonimines to expand the scope of the aqueous Barbier-type allylation reaction (Chapter 2); the stereoselectivity study for the stereocontrol in the aqueous Barbier-type allylation of sulfonimines (Chapter 3); the search for new nucleophiles to generate water-compatible organometallic species to expand the chemistry beyond the boundary of allylation transformations (Chapter 4 and 5); the development of polyfunctional organoindium reagents for the synthesis of dienol compounds and its application in organic synthesis (Chapter 6). The following discussion will focus on the remaining challenges and future perspectives for the development in this chemistry.

7.2 Stereochemical Control in Aqueous Media: *Can We Do It Better?*

It is a persistent challenge to perform reactions in aqueous media in a highly stereochemical-controlled manner. Allylindium species is presumably a water-solvated organometallic reagent and its diastereoselectivity behavior has been extensively

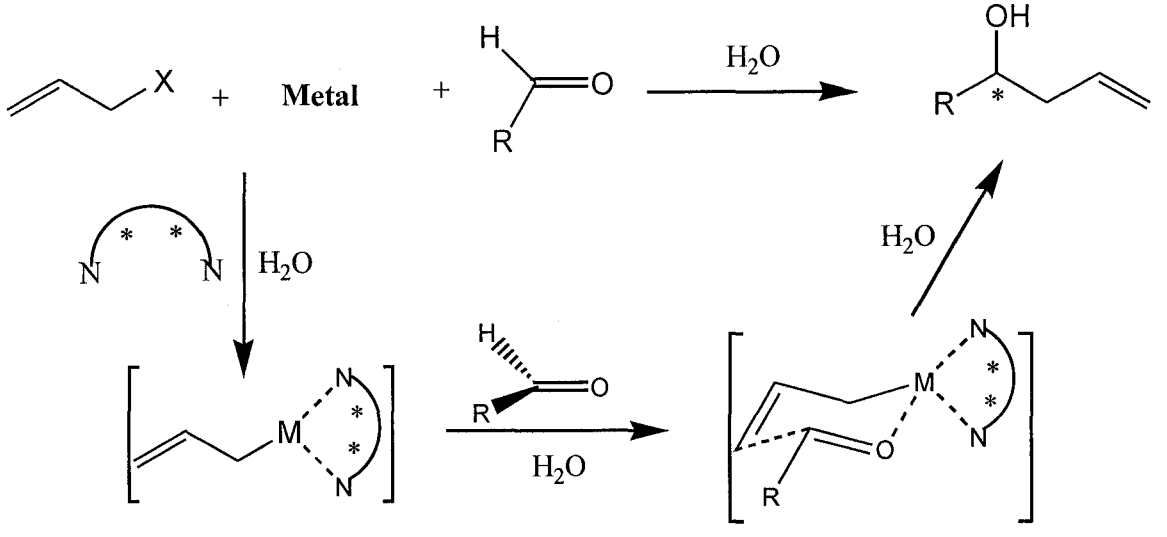
examined in the allylation of both C=O and C=N electrophiles. However, to make this reagent a truly effective tool for highly stereospecific carbon-carbon formation in synthesis,[2] especially in aqueous media, more efficient strategies and more potent stereo-auxiliaries are still needed to be developed and to be explored. For example, in Chapter 3, we have demonstrated that the aqueous allylindation of benzenesulfonylimino-acetic acid menthol ester showed rather poor diastereoselectivity. The poor stereo-selectivity is presumably due to the weak chiral induction of (-)-menthol group. Therefore, it would be interesting to introduce a more efficient chiral auxiliary for the stereo control in the reaction. (Scheme 7.1)



Scheme 7.1

In comparison with numerous asymmetric allylation strategies by using allylmetal reagents such as organoborane and organotin in organic solvents,[3] the aqueous

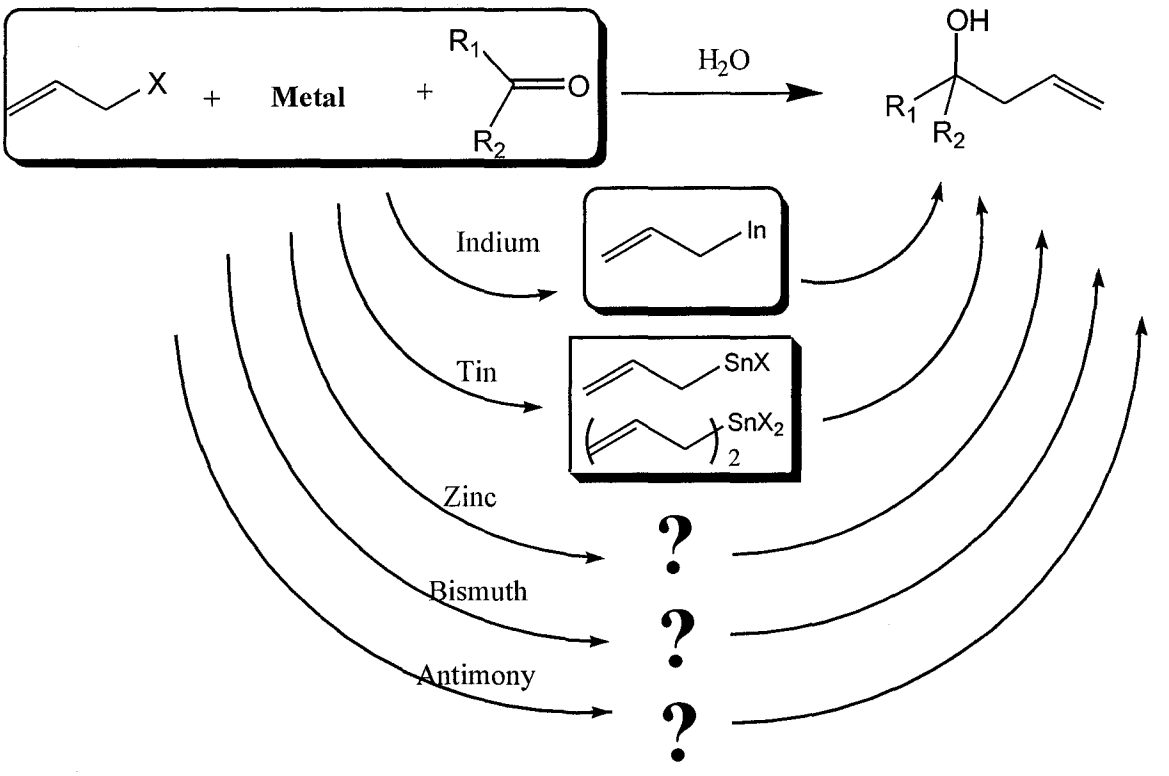
asymmetric Barbier-type allylation reaction is still unproductive. The stereo-control in this reaction is obviously hampered by the fact that in the transition state, metal atom might be solvated in presence of water. Any attempt for the chiral modification of the central metal atom[4] will face the competitive chelation effect from water. However, an encouraging result was reported recently by Loh's group,[5] in which (S, S)-2,6-bis(4-isopropyl-2-oxazolin-2-yl) pyridine was successful employed as chiral auxiliary. The result implied that chiral base might be suitable for the aqueous stereo-control, presumably due to the strong chelation between indium and nitrogen atom to compete with solvation in aqueous media. This might also suggest further examination of other nitrogen-containing chiral ligands for the efficient enantioselective control in the metal-mediated aqueous Barbier-type allylation reactions.[6] (Scheme 7.2)



Scheme 7.2

7.3. The Nature of Things. *Can We Know more and better ?*

In every aspect of real life, the clearer we understand, the better we can perform. So is it in chemistry. When the aqueous Barbier-type organometallic reaction was first discovered, three different mechanisms were suggested: organometallic intermediate, radical intermediate and SET processes on metal surface. Although the nature of organotin[7] intermediates or organoindium[8] intermediates have been elucidated in the tin or indium-mediated aqueous Barbier-type allylation reaction, the puzzle of the nature of the aqueous Barbier type allylation reaction is still far from resolved. In some cases, a parallel process, such as the SET process, could not be ruled out from the described mechanism. Moreover, it has been observed that different metals actually proceed through different processes in the metal-mediated aqueous Barbier-type allylation reactions. For example, in zinc-mediated reactions, no organozinc intermediate has been observed. In fact, zinc showed reactivity and selectivity different from indium or tin in many cases.[9] We believe that we may take advantage of the different reaction behavior among the metals to make the reaction more controllable and more useful in organic synthesis. However, it is still a challenge to understand the real process of the aqueous Barbier type allylation reactions mediated by metals such as zinc, bismuth, antimony, etc. — *Can we know more and better?* (Scheme 7.3)

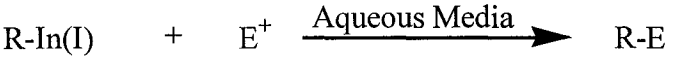


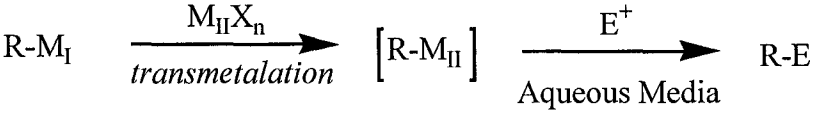
Scheme 7.3

7.4. The Expansion of the Scope of Aqueous Organometallic Reactions. *How Far Could We Go?*

Despite the painstaking efforts, it is still a long way to go in the expedition of aqueous organometallic reactions. The major effort, up to now, is still focused on the transformations under the Barbier-type conditions. Although the Barbier-type conditions provide a convenient way to generate organometallic reagents for the reaction, the deficiency of this condition is obviously due to the presence of metal powder that reductive functional groups usually will not be tolerated. From this point, the examining of some water-compatible organometallic compounds like organoindium(I) compounds and organotin compounds might potentially provide an opportunity to expand the scope of this chemistry.[10] Moreover, the aqueous transmetalation might also be employed as an

efficient strategy to generate versatile water-compatible organometallic reagents.[11](Scheme 7.4)

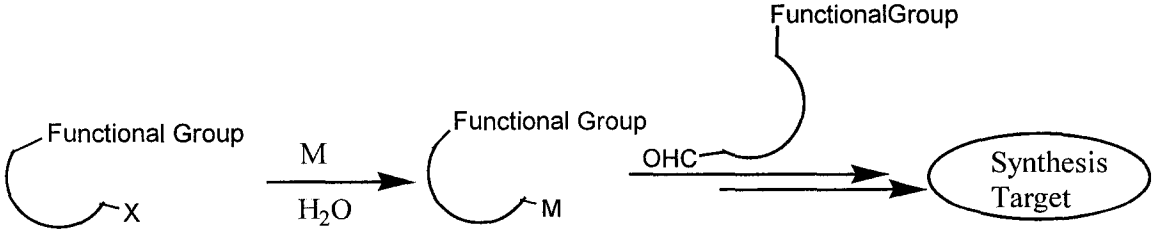




Scheme 7.4

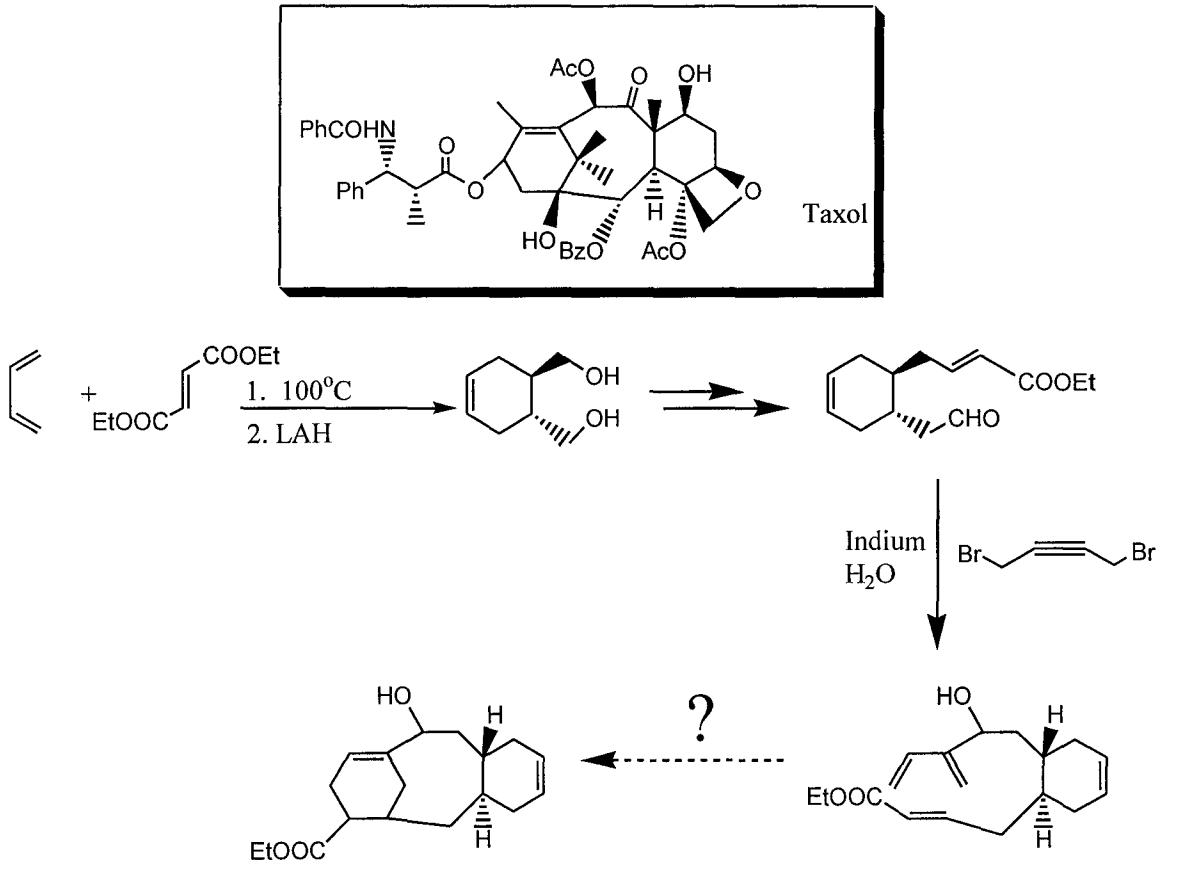
7.5. Polyfunctional Organometallic Reagents in Organic Synthesis

The complexity of organic target molecules is constantly increasing in recent organic synthesis.[12] Novel strategies, which allow more efficient formation of new carbon-carbon bonds between functionalized moieties, are imminently needed. Conventional approaches using extensive protecting-group strategies are less satisfactory because of mediocre atom economy. It is our belief that the aqueous chemistry is capable of developing efficient strategies for organic synthesis. Upon this point, more water-tolerable polyfunctional organometallic reagents need to be developed.[13]



Scheme 7.5

We have demonstrated the indium-mediated aqueous coupling reaction of 1, 4-dibromo-but-2-yne with aldehydes as a concise strategy to synthesize 1,3-dienol compounds,[14] which have enormous potential in total synthesis. It may provide a pathway for the synthesis of the taxoid skeleton. At the present stage, we are working on the intra-molecular Diels-Alder reaction on the construction of an (8,6)-fused ring. A suitable condition for this cyclization might be found. (Scheme 7.6)



Scheme 7.6

In summary, in the pursuit of atom economy and environmental benign methodologies for organic synthesis, aqueous organometallic reactions hold significant potential for these purposes. It is still a challenge to perform reaction in a highly stereo-selective, especially in an enantio-selective manner in aqueous media. We still need to

expand the scope of metal-mediated aqueous organometallic reactions. The key is to understand the nature of these metal-mediated aqueous organometallic reactions at a profound level. With the advantage of the active proton functional compatibility, this chemistry has demonstrated its efficiency in the synthesis of carbohydrate-related natural products.[15] The prospective is that more versatile polyfunctional organometallic reagents could be developed and more applications of this chemistry could be demonstrated in future organic synthesis.

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