Organometallic-Type Reactions in Aqueous Media: The Issue of Regio-, Chemo- and Stereoselectivity

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Abstract

The regio- and diastereoselectivity in the coupling of γ-substituted allylic bromides with aldehydes mediated by indium in water were examined and found to be dependent on the steric effect of the substituents on both the allylic bromides and the aldehydes.

Despite the efficiency with which indium mediates carbon-carbon bond formation between allyl halides and aldehydes in an aqueous environment, it is not without short-comings. Nitro-functionalised aldehydes were found to be susceptible to the reductive conditions of this aqueous indium Barbier-Type reaction. In this connection, bismuth was found to chemoselectively mediate the coupling of allyl halides with aldehydes in water in the presence of tetrabutylammonium halides.

The indium Barbier reaction in an aqueous medium was extended to include propargylic bromides. The coupling of aldehydes with propargylic bromides gave regioselectively either the homopropargyl alcohol or the α-allenic alcohol depending on the γ-substituent of the propargylic bromides.

The regio- and stereochemical course of the indium-promoted coupling of γ-substituted allylic halides with aldoses (water soluble carbohydrates) has been investigated. The stereoselective generation of two new contiguous stereogenic centres has been applied to the synthesis of novel 2-substituted carbohydrates. The stereoselectivity of the reaction was explained on the basis of chelation of the allyl indium species with the α-hydroxycarbonyl function. This gives syn selectivity for the Cγ-Cβ diol function in the product. The relative stereochemistry of the Cβ-Cα linkage in the product is governed by the preferred geometry of the allyl indium species.

Résumé

Nous avons étudié les régio- et stéréosélectivités de réaction de bromures d'allyle γ-substitués en présence d'indium dans l'eau, et avons trouvé une dépendance en fonction des effets stériques des substituants sur les bromures allyliques et sur les aldéhydes.

Malgré l'efficacité avec laquelle l'indium induit la formation de liaisions carbone-carbone entre halogénures d'allyle et aldéhydes en milieu aqueux, certaines limitations demeurent. Des aldéhydes portant une fonctionalité nitro sont sensibles aux condition réductives de cette réaction de type Barbier en présence d'indium en solution aqueuse. Dans le même sens, nous avons trouvé que le bismuth pouvait favoriser le couplage d'halogénures d'allyle avec des aldéhydes en milieu aqueux de façon chimiosélective, en présence d'halogénures de tétrabutylammonium.

La réaction de Barbier en présence d'indium a été étendue aux bromures de propargyle. Le couplage d'aldéhydes avec des bromures de propargyle a donné de façon régiosélective soit les alcools homopropargyliques soit les alcools alléniques correspondants, suivant le substituant γ du bromure de propargyle.

Nous avons ensuite étudié la régio- et stéréochimie du couplage d'halogénures d'allyle substitués en γ en présence d'indium avec des aldoses (carbohydrates solubles dans l'eau). La création stéréosélective de deux nouveaux centres stéréogéniques contigus a été appliquée à la synthèse de nouveaux carbohydrates substitués en 2. La stéréosélectivité de la réaction a été interprétée par le biais d'une chélation entre l'intermédiaire allyle indium d'une part et la fonction α-hydroxycarbonyle d'autre part. Cela produit une sélectivité syn pour la fonction diol en Cγ-Cβ sur le produit. La stéréochimie

relative du lien Cβ-Cα sur le produit est gouvernée par la géométrie préférée par l'intermédiaire allyle indium.

Contribution To Original Knowledge

Metal-mediated Barbier-type allylation reactions of carbonyl compounds in aqueous media using zinc, tin and more recently indium have been developed. Indium has not been much explored in organometallic reactions. It was only recently that indium has been used in Reformatsky reactions, allylation and cyclopropanation of carbonyl compounds. Despite the growing use of indium metal in organic synthesis, little was known about the regio- and diastereoselectivity of these reactions in water as solvent.

The aqueous indium-mediated coupling of aldehydes with simple allylic halides has been extended to γ-substituted allylic systems and the factors governing regio- and diastereoselectivity were shown to be largely dependant on the steric effects of the substituent in both the aldehydes and allylic halides.

The difficulty associated with the susceptibility of the nitro- group of nitro-functionalised aldehydes to the reductive conditions of the aqueous indium-Barbier-type allylation was circumvented by using bismuth metal in the presence of tetrabutylammonium halides.

A new methodology has been developed for the selective synthesis of α-allenic alcohols using indium-promoted propagylation of carbonyl compounds in aqueous media.

Finally, the regio- and stereoselective aspects of the aqueous indium-mediated allylation have been applied to the synthesis of novel 2- and 3-substituted carbohydrate homologues.

Table of Contents

List of Abbreviations

Ac	acetyl
Bn	Benzyl
Bu	butyl
cat	catalytic
COSY	homonuclear correlation spectroscopy
Cp	cyclopentadienyl
d	doublet
D	Dextrorotatory
de	diastereomeric excess
DCB	2,6-dichlorobenzyl
DIBAL-H	diisobutylaluminum hydride
DMA	N, N-dimethylacetamide
DMF	N, N-dimethylformamide
DMI	1,3-dimethylimidazolidinone
DMP	dimethoxypropane
DMPU	N, N-dimethylpropyleneurea
DMSO	dimethylsulfoxide
Et	ethyl
h	hour
i-Pr	isopropyl
IR	infrared spectroscopy
KDN	ketodeoxynonusolonic
KDO	ketodeoxyoctusolonic
LiTMP	lithium N,N,N,N-tetramethylpiperidide

LDMAN	lithium N, N -dimethylaminonaphthylide
Me	methyl
Ms	mesylate
mp	melting point
MOM	methoxymethyl
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
Ph	Phenyl
Py	pyridine
SET	single electron transfer
TBS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TMEDA	N,N,N,N-tetramethylethylenediamine
TMS	trimethylsilyl
Tf	triflate
Ts	p-toluenesulfonyl

Chapter 1

Introduction

Organometallic reagents are among the preferred tools of modern organic synthesis. What makes them so appealing is a combination of valuable properties : *versatility*, *reactivity* and *selectivity*. Selectivity means preference for a given reaction channel if there is a choice among several related ones. However, there has recently been an increasing interest in performing a wide variety of organic transformations by direct reaction of metals with an organic substrate. This represents an elegant and advantageous approach that avoids the use of sensitive, toxic and expensive organometallic reagents, as well as the ineluctable and often lengthy transmetallation step starting from other organometallics, particularly the more reactive alkyllithiums or Grignard reagents. These one step protocols have become popular among chemists, although a previous activation or depassivation of the metal surface is sometimes required.

Most metals of the Periodic Table have been utilized for their synthetic purposes with varied usefulness and selectivity. Some striking properties of certain elements or organometallics have now been rediscovered, and such substances readily incorporated into the vast armoury of synthetic method development. The ability to perform organic transformations by direct reaction of metals with organic substrates, thereby generating the organometallic reagent *in situ*, is described as an *Organometallic- Type Reaction*.

Organometallic compounds, amongst the most useful reagents in organic chemistry, usually are prepared in anhydrous solvents due to the rapidity of protonolysis. The presence of water is also known in most cases to inhibit the formation of the reagent. Nevertheless, since the discovery of the dramatic rate

accelerations in various Diels-Alder cycloadditions in aqueous solution,[1] water has been considered as a promoting medium for diverse reactions. Water is a very special medium affecting not only reaction kinetics, but also stereoselectivity.[2]

Previously, water as a solvent was for the most part ruled out from studies for several reasons. Among them were the insolubility of the reactants and the incompatibility of the intermediates with water. However, many biochemical processes occur in the presence of water, and the diversity of the reaction *in vivo* prompted chemist to investigate the potential of water as a solvent. As a matter of fact, the hydrophobic effect, a principal force determining the folding of protein and nucleic acids, and the binding of enzymes to substrates, has been utilized to rationalize the kinetic and stereochemical course of the Diels-Alder reaction.[2]

Recently, the possibility of conducting organometallic-type reactions in aqueous medium for the formation of cabon-carbon bond has been an area of considerable interest to the organic community.[3,4] Such reactions offer the following advantages: (1) There is the practical convenience of not having to handle inflammable and anhydrous organic solvents. (2) The tedious task of protection-deprotection of certain functional groups may sometimes be avoided. (3) Water-soluble compounds such as carbohydrates can be reacted directly.

The choice of metals for organometallic reactions in aqueous media is quite limited. The reactive alkali and alkaline earth metals cannot be used because of their vigorous reaction with water itself. Metals which form aqueous insoluble oxides are unlikely candidates. So far, the most commonly used metals in aqueous organometallic reactions are zinc and tin.[5,6] Very often, acid catalysts, heat or sonication are required to induce reactions to occur.

In this connection, indium metal offers some intriguing possibilities. Compared to other metals, indium has not been much explored in organometallic-type reactions.[7] It was only recently that indium has been used in Reformatsky reactions,[8] allylations[9] and cyclopropanations[10] of carbonyl compounds. In addition, what makes indium chemistry particularly useful and attractive, is that it closely parallels the chemistry of certain transition metals and heavier main group elements without the problems associated with their handling.

Despite the growing use of indium metal in organic synthesis, little is known about the regio-, chemo and stereoselectivity of these reaction in aqueous media. Thus, it is the goal of this dissertation to examine these aspects of the indium-mediated reactions in aqueous media along with their application to carbohydrate synthesis.

Although indium metal seems to be the most appropriate metal for aqueous mediated reaction, it is not without shortcomings. The use of bismuth metal as an alternative metal when problems of chemoselectivity with indium arise will also be explored.

Prior to the discussion of the regio-, chemo and stereoselective aspects of indium-mediated reactions in aqueous media, a literature survey of metal mediated reactions in organic and aqueous solvents will be given, highlighting the regio, chemo- and stereochemistry where appropriate.

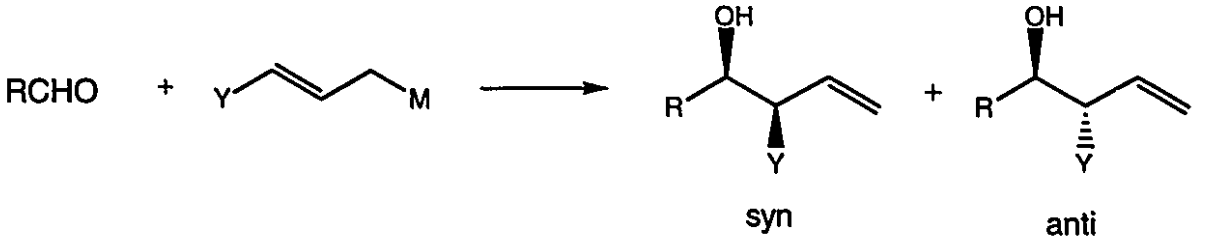
1.1 Metal-mediated reactions in Organic Solvents

The development of carbon-carbon bond forming reactions in organic chemistry constitutes the very essence of organic synthesis. Since the advent of the organometallic or metal-mediated reactions , this method has been shown to be one of the most efficient ways of effecting cabon-carbon bond

construction. Despite the wide variety of such carbon-carbon bond forming processes that exist in organic solvents, the most prominent ones include allylations and Reformatsky reactions.

A. Allylation

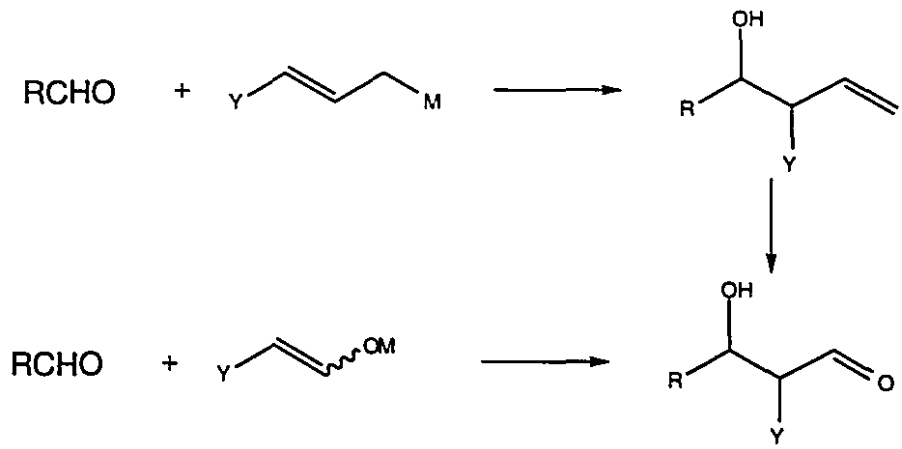
Prior to the late 1970s, the interest in allylic organometallic compounds lay primarily in their structural determination.[11] Studies on the reaction of allyl metals with the electrophiles were carried out in an attempt to distinguish between competing reaction sites (*regioselectivity* or *positional selectivity*) of the allylic unit (S_E2' or S_E2). Beginning in the late 1970s, a new emphasis appeared in this field where a significant synthetic interest began to emerge in the control of the syn-anti stereochemistry of C-C bond formation in the reactions of allylmetals with aldehydes and ketones (Scheme 1.0).



Scheme 1.0

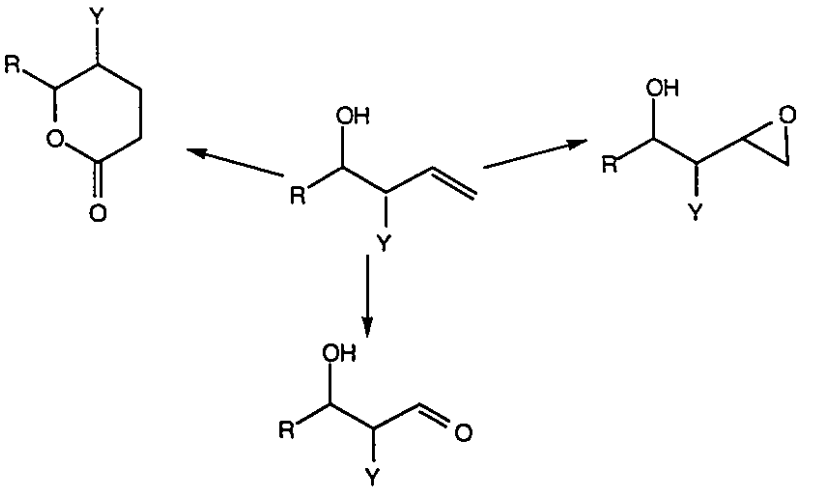
The widespread use of allylic organometallics in stereocontrolled organic synthesis appears to have been triggered by three papers: Heathcock's discovery that the Hiyama (E)-crotylchromiun reagent[12] undergoes highly anti-selective addition to aldehydes;[13] Hoffmann's finding with (Z)-crotylboronates produces syn-homoallylic alcohols stereoselectively;[14] and Yamamoto's discovery that the Lewis acid mediated reactions of crotyltins with aldehydes produces syn homoallylic alcohols regardless of the geometry of the double bond of the allylic tins.[15]

The aldol reaction, a synthetically useful reaction, constitutes one of the most fundamental C-C bond construction in biosynthesis. Interestingly however, the reaction of allylic organometallic reagents with aldehydes is synthetically analogous to the aldol addition of metal enolates, since the resulting homoallylic alcohol can be easily converted to the aldol (Scheme 1.1).



Scheme 1.1

Furthermore, allylmetal addition have significant advantages over aldol reactions since the alkene moiety of the homoallylic alcohol, which may be readily transformed into aldehydes, may undergo a facile one carbon homologation to δ-lactones via hydroformylation, or may be selectively epoxidized to introduce a third chiral centre (Scheme 1.2). Accordingly, the allylic method has become one of the most useful procedures for controlling the stereochemistry in acyclic systems.



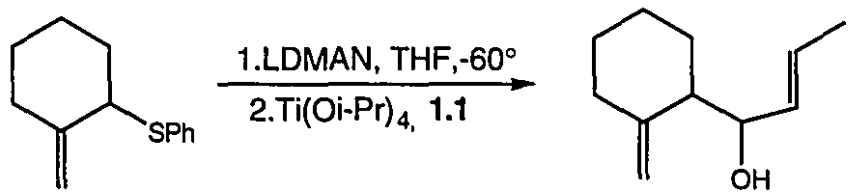
Scheme 1.2

The subsequent discussion in this section will survey some recent advances in the allylation reactions of carbonyl electrophiles such as aldehydes and ketones. The allylation reactions involve the nucleophilic (or radical) attack of the allylic groups on the carbonyl electrophiles. This transformation of carbonyl compounds to homoallylic alcohols has employed various types of methods using allylic metal reagents. The metals that have been exploited include Li, Mg, Ba, Zn, Sn, Al, Pb, Ni, Cr, Mn, Bi, Sm, Ti, Zr, Ce and In.

A. I Allylic Lithium Reagents

Alkyl and aryllithiums are usually prepared by halogen-metal exchange, but allyllithiums are not available by this route because of competing substitution reactions. The traditional routes to allyllithium are (1) transmetallation of the corresponding allyltins and allyllead by using alkyllithiums,[16] (2) ether cleavage with lithium or lithium biphenyl,[17] (3) the reaction of alkyllithium with allyl methyl and allyl phenyl selenides[18] or (4) metal reduction[19] of the appropriate allyl halide. Recently, it has been shown that the aromatic radical anion induced reductive lithiation of allyl phenyl thioether is a versatile and general method for generating allyllithiums.[20]

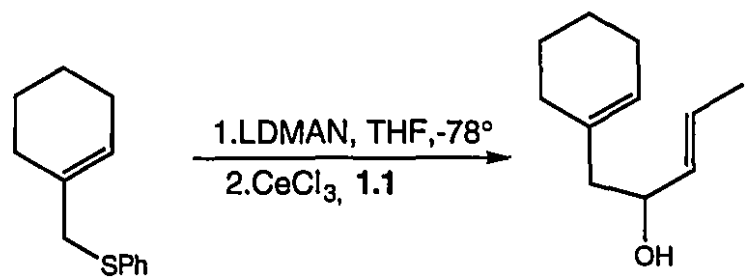
In the case of unsymmetrical allyllithiums, regiochemical control in subsequent reactions with electrophiles are essential to their utility. Because of the poor regio- control associated with unsymmetrical allyllithiums, reaction with aldehydes in THF are usually nonselective with a slight preference for attack at the most substituted allyl terminus. To enhance the regioselectivity of these reactions, Lewis-acid such as $Ti(OiPr)_4$ can be added. For example, treatment of the allyllithum derived from **1.0** with titanium tetraisopropoxide followed by crotonaldehyde **1.1**, resulted in high yields of two diastereomers (9:1) as a single regioisomeric 1,2 addition product **1.2** (Eq. 1).[21]



(1)

1.0 **1.2**

On the other hand, treatment of an unsymmetrical allylithium with cerium (III) chloride, followed by crotonaldehyde, results mainly in the addition of the least substituted terminus to the carbonyl group;[22] the ratio of **1.4** to **1.2** was 18:1.

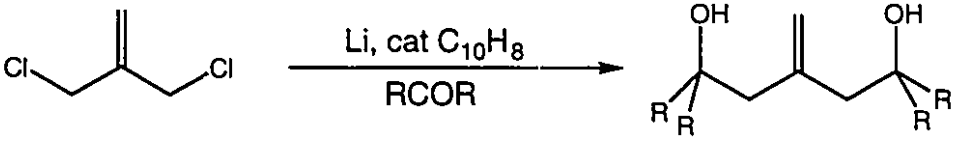


(2)

1.3 **1.4**

This novel regio selectivity has made possible a highly efficient synthesis of the pheromone of the comstock mealybug, a very significant agricultural pest.[23]

Lithiation of 3-chloro-2-(chloromethyl) propene is catalysed by naphthalene. The reaction of an equimolar amount of the chloride and the carbonyl compound with an excess of lithium powder and a catalytic amount (6%) of naphthalene in THF at -78°C leads to the corresponding diols in a Barbier-type process (Eq. 3).[24]

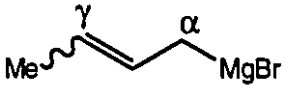


(3)

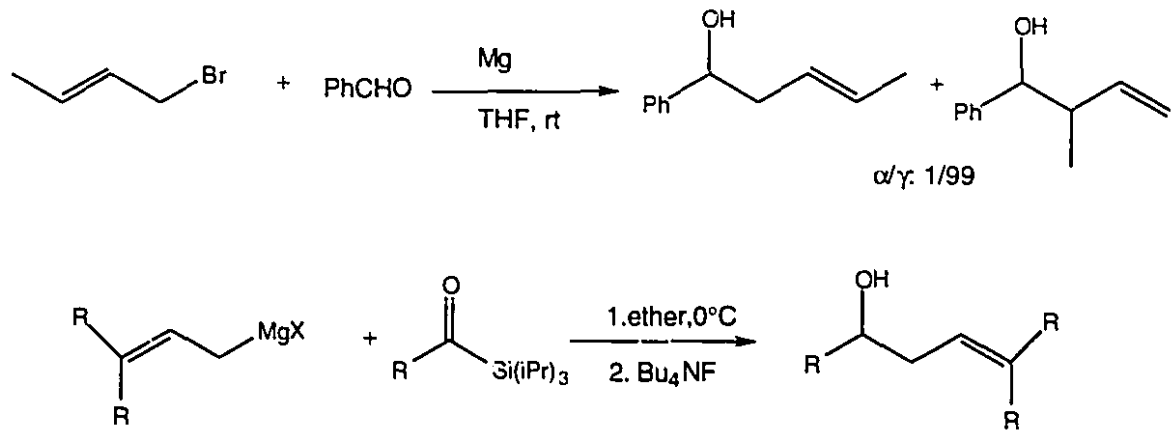
A. II Allylic Grignard and Allyllic Barium Reagents

Allyl magnesium reagents (Allyl Grignard reagents) are easily prepared by direct reaction of the metal with the allyl halide. Diethyl ether is the solvent most commonly used in this preparation, but THF works as well. A minor problem is the propensity for the Grignard reagent to couple with unreacted halide (Wurtz-type coupling).

The isotopic perturbation technique has been used to distinguish between the σ– and π- bond structures of allyl and crotyl magnesium and lithium reagents.[25] The ^{13}C NMR spectra of the deuterated crotyl reagents demonstrate that the crotylmagnesium reagents are σ structures in which the metal is attached to the primary carbon whereas the crotyllithium reagents are π- structure in which the metals are bonded to carbon α and γ of the allylic system as shown. The carbon-metal length in crotyllithium are unequal.

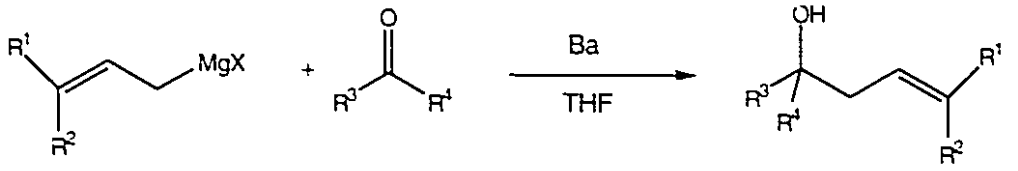


The reaction of unhindered carbonyl compounds with substituted allylic Grignard reacts regioselectivity to give the γ adduct (Scheme 1.3). However, with hindered ketones such as di-tert-butyl ketone and triisopropylsilyl ketones, the α adduct is obtained (Scheme 1.3). Despite the tendency of unhindered carbonyl compound to react with allyl Grignard to give the γ adduct, the reaction in the presence of $AlCl_3$ at -78°C give predominantly the α-adduct .[26]



Scheme 1.3

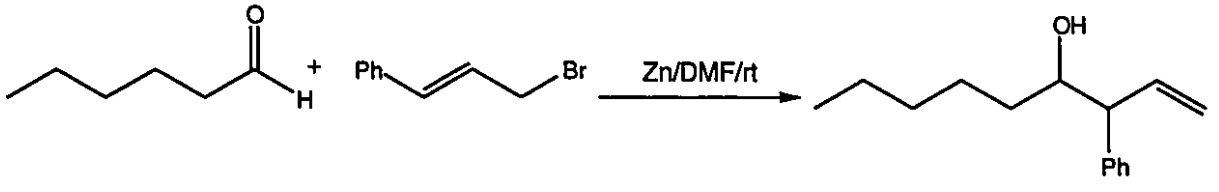
Allylbarium can be prepared directly with various allylic chloride, and the regio- and stereoselective allylation of carbonyl compounds can be accomplished using these allylmetals. Highly reactive barium was readily prepared by the reduction of barium iodide with lithium biphenylide (2 eq) in dry THF at room temperature. The allylic barium reagent reacted with a variety of aldehydes and ketones cleanly at -78°C to produce the homoallylic alcohol with remarkably high α–selectivity and retention of the stereochemistry of the starting halide (Scheme 1.4).[27]



Scheme 1.4

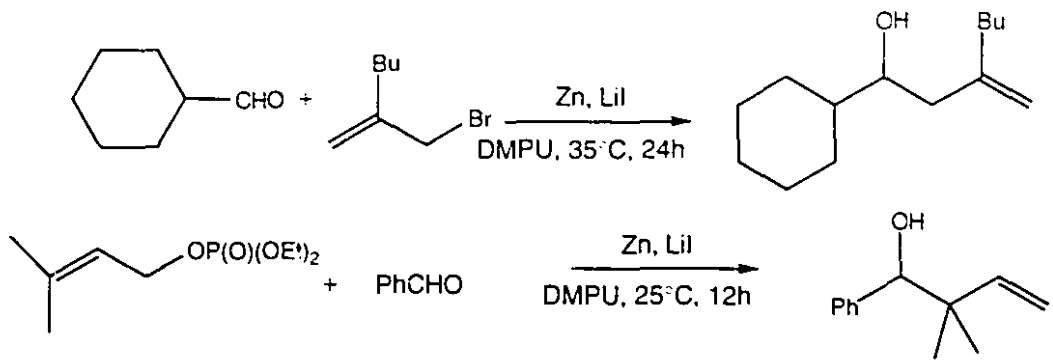
A. III Allylic Zinc Reagents

The general preparation of allylic zinc halides has been carried out in ether or THF and these allyl metal reagents show a reactivity comparable with Grignard reagents. Alcohols can serve as solvents for the generation and addition of allylic zinc halides to aldehydes and ketones. Zinc promoted transformation of carbonyl compounds to the homoallylic alcohols proceeds quite smoothly using DMF as a solvent.[28] Furthermore, it has been reported that the zinc-mediated reaction of hexanal with cinnamyl bromide carried out in THF did not give the allylation product[29] whereas it proceeds very smoothly in DMF giving regioselectively, the γ-adduct with a 3 : 1 syn-anti diastereoselectivity (Scheme 1.5).



Scheme 1.5

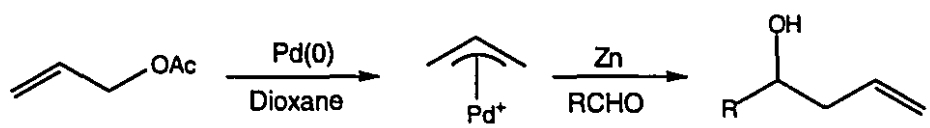
The use of mesylates or the more stable allylic phosphates allow the generation of the corresponding allylic zinc reagent under Barbier conditions in the presence of zinc, a catalytic amounts of LiI, and the carbonyl compound in DMA or DMPU, leading to homoallylic alcohols in excellent yields (79-95%) (Scheme 1.6).[30]



Scheme 1.6

Regioselective α allylation has been accomplished using tri-isopropylsilyl ketones and substituted allylic zinc bromides. The reaction of benzaldehydes with crotyl and prenyl zinc bromides give the γ-allylation product exclusively, whereas the use of silylated ketone as an electrophile followed by desilylation affords only the α product .[26]

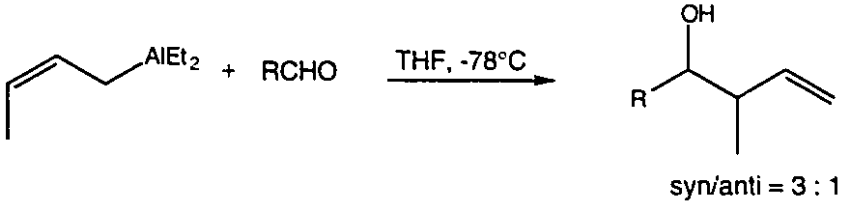
Allylic acetates are reduced by zinc in the presence of a catalytic amounts of $Pd(PPh_3)_4$ to serve as nucleophilic allylating agents, which reacts with aldehydes to afford the homoallylic alcohols in good yields (Scheme 1.7).[31] The diastereoselectivity is in most cases syn, but low. Aldehydes and ketones react with allylic bromides in the presence of Cp_2TiCl_2 (cat)/ Zn system at room temperature to give homoallylic alcohols in high yields but with low diastereoselectivity in the case of crotyl and cinnamyl bromides.[32]



Scheme 1.7

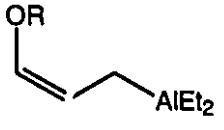
A. IV Allylic Aluminum and Allyllic Indium Reagents

Allyic aluminum reagents, generated by the reaction of allylpotassium with dialkylaluminum halides, react with aldehydes to give good regio- and diastereoselectivity. For example, Z-crotyldiethylaluminum, prepared from Z-crotyl potassium and diethylaluminum chloride, reacts with aldehydes to give regioselectivity, the γ adduct with good stereoselectivity (Scheme 1.8).[33]



Scheme 1.8

γ-Alkoxysubstituted allyldiethylaluminum reagents **1.5** are prepared by the treatment of the corresponding alkoxylithiums with Et_2AlCl in THF at -78°C. The aluminium reagent **1.5a** provides syn isomers with 9-11:1 diastereoselectivity in reactions of aldehydes at -78°C, whereas **1.5b** gives 4 : 1 syn selectivity in the reaction with acetophenone.



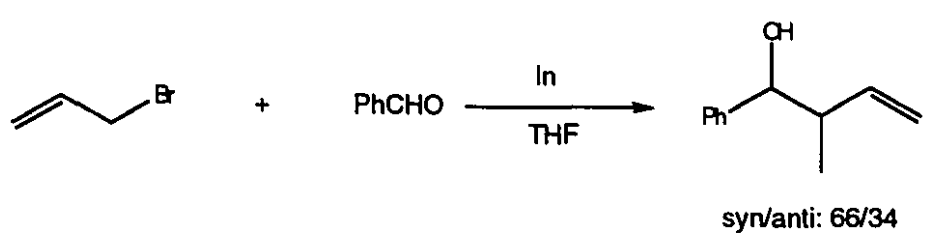
1.5 **a**; R=Me
b; R=$MeOCH_2$

The reaction of metallic indium with alkyl halides, either bromides or iodides, affords mainly the corresponding sesquihalides, $R_3In_2X_3$. Further treatment of these with KBr or KI enables the isolation of the dialkylindium halides.[34] The process works well with alkyl halides but sluggish reactions are

in higher polarity organic solvents such as THF or DMF at room temperature. Under these conditions, the insertion of indium takes place regioselectively at the α carbon of the allylic halide. In contrast to allylic magnesium and lithium reagents, the ailylic indium reagents do not react with allylic halides, thus avoiding the undesirable Wurtz-type by-products which are usually formed in the preparation of allyllithium and Grignard reagents. Although such allylindium compounds can be isolated as viscous oils, both their preparation and further coupling with an organic substrate can be conducted in an easy one-pot procedure.

Indium powder-mediated Barbier-type allylations of a variety of ketones and aldehydes afford excellent yields of the corresponding homoallylic alcohols.[9] Allyl bromides and iodides are equally reactive, but chlorides gave lower yields and required prolonged reaction times. Even, the less reactive allyl phosphates do react with carbonyl compounds in the presence of indium plus lithium iodide.

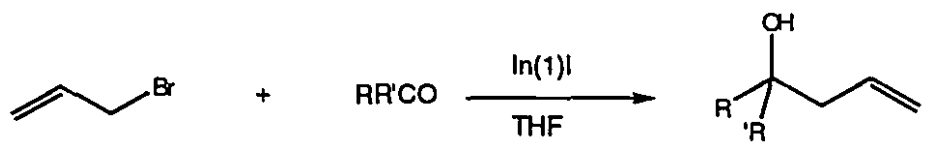
Crotyl bromide reacted with benzaldehyde under the indium mediated conditions to give the branched homoallylic alcohol regioslelectively, but the diastereoselectivity was low; syn : anti = 66 : 34 (Scheme 1.9). Cinnamyl bromide and prenyl bromide also provided the branched alcohol exclusively. Furthermore, esters and cyano groups do not undergo allylation under these conditions and the hydroxyl group remains unaffected as well.



syn/anti: 66/34

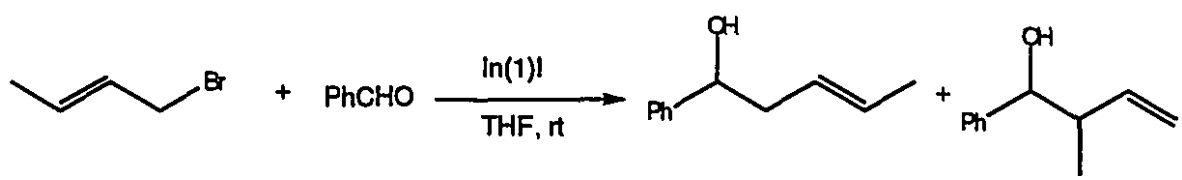
Scheme 1.9

In addition to indium metal, indium (I) iodide has been shown to be useful in generating allyl indium dihalide reagents in THF which can be subsequently coupled to aldehydes and ketones. These indium reagents have a moderate nucleophilicity towards various electrophiles under mild conditions and display high regio- and chemoselectivity.[35] The Barbier allylation of carbonyl compounds mediated by indium (I) iodide gave the homoallylic alcohols in good yield. Under these conditions, THF was the solvent of choice as DMF gave the products in lower yields(Scheme 1.10).



Scheme 1.10

Although α, β-unsaturated carbonyl substrates are allylated exclusively with a 1,2-mode of addition, the regioselectivity of these reactions are lower than those with indium metal as a mediator. For example, indium (I) iodide-mediated coupling of benzaldehyde with crotyl bromide produces mixtures derived from both α and γ-coupling (Scheme 1.11).



syn/anti: 48/52

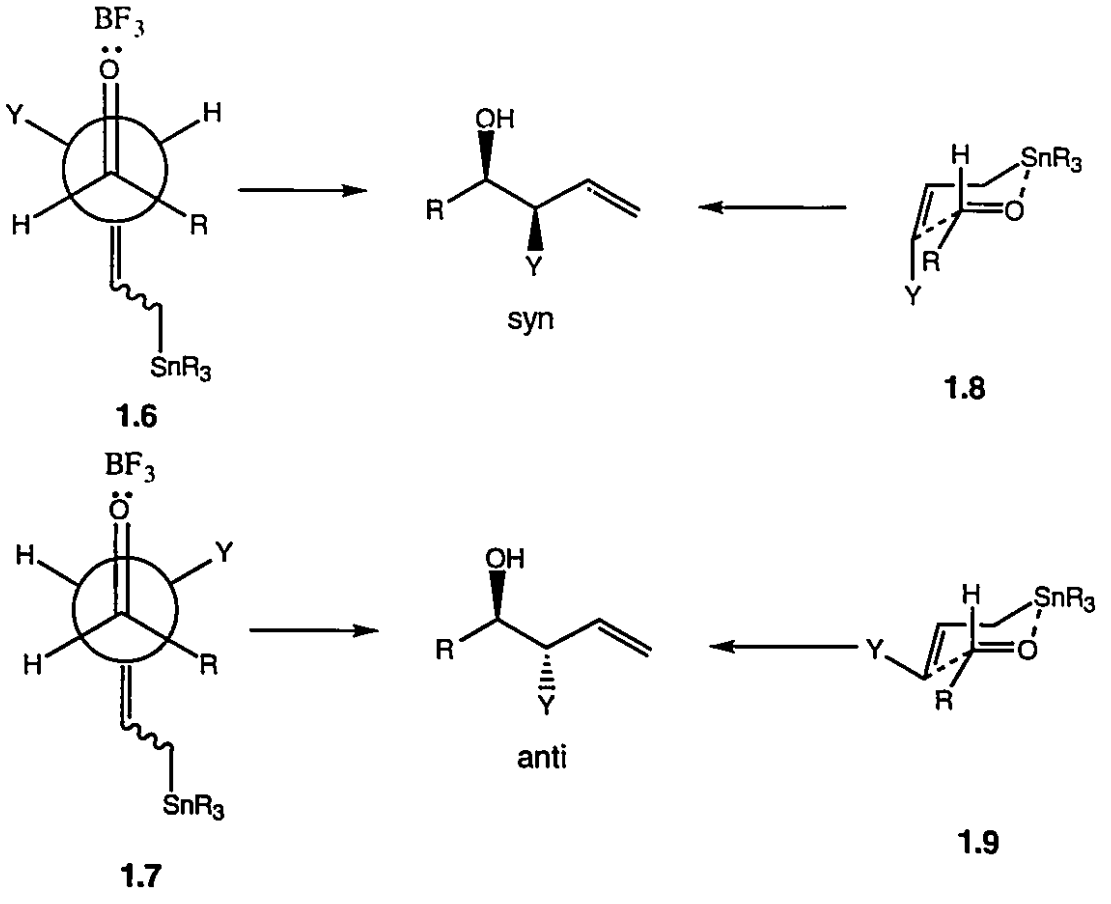
Scheme 1.11

A. V Allylic Tin and Lead Reagents

Allylic tin reagents are one of the most widely used allylmetal reagent in organic chemistry. These reagents can be prepared from the corresponding allyl halide by reaction with trialkyl- or triaryltin lithium compounds. Allylic tin reagents react with carbonyl compounds in a regioselective and stereoselective manner. The Lewis acid mediated reactions of allylic tins have previously been shown to produces syn homoallylic alcohols regardless of the allyl geometry.[15] However the recent reinvestigation of the Lewis acid-mediated reaction of substituted allyltin reagents toward aldehydes gave regioselectively the γ–adduct with anti- diastereoselectivity when $ZnCl_2$ is used as the Lewis acid. In contrast, the BF_3-mediated reaction gave the γ-adduct with syn-diastereoselectivity.

The stereochemistry in thermal reactions of allylic tin derivatives generally depends upon the geometry of the allyl unit. The E-allylic isomers produce the anti-alcohols while the Z-isomers afford the syn-alcohol.

The syn diastereoselectivity of BF_3-mediated reactions can be explained by the acyclic transition state shown in Scheme 1.12. BF_3 coordinates to the carbonyl oxygen, preventing the coordination of the metal to the oxygen atom. Consequently, among several possible transition states, the conformation of **1.6** leading to the syn isomer must be more favorable for steric reasons than **1.7** which produces the anti isomer

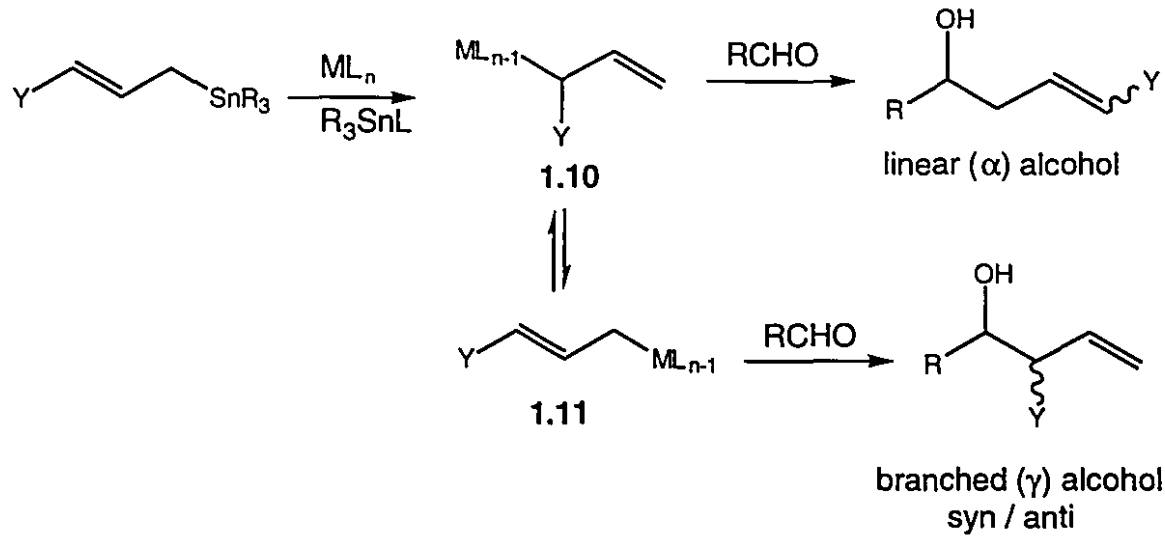


Scheme 1.12

It is easily understood that the geometry of the allyl unit does not exert an important role in stabilizing the transition states. On the other hand, the thermal or high-pressure reaction proceeds through a six-membered cyclic transition states **1.8** and **1.9**. It is widely accepted that the Z-isomer produces the syn-homoallyl alcohol, while the E-isomer affords the anti- alcohol in reactions via the cyclic transition state.

The Lewis-acid mediated reactions may proceed via addition of a Lewis acid aldehyde complex as shown in Scheme 1.12 or via transmetalation to yield a reactive allyl metal halide which then reacts with the aldehyde. The reaction pathway depends on the Lewis acid, the aldehyde, the stoichiometry of reactants, the order of addition and the reaction conditions; these will determine

the regio (linear or branched) and stereochemistry (syn or anti) of the product (Scheme 1.13).

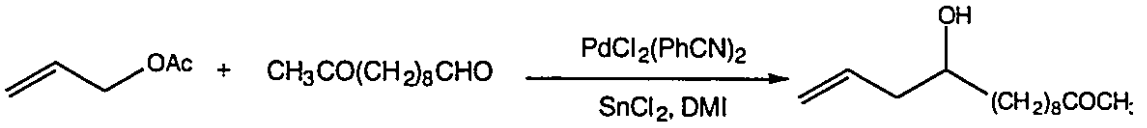


Scheme 1.13

If transmetalation is involved, the product may consist of a mixture of regioisomers due to allylic rearrangement of the allylmetal halide intermediate. For example, the reaction of crotyltributyltin with aldehydes such as benzaldehyde, propanal, butanal, pentanal, and decanal in the presence of $AlCl_3$/i-PrOH produces the linear adduct predominantly or exclusively, while the reaction in the presence of Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3.OEt_2$ affords the branched product exclusively.[36] It is interesting to note that less reactive aldehydes or ketones such as crotonaldehyde, isobutyraldehyde and acetophenone give the branched alcohol exclusively in the case of $AlCl_3$/i-PrOH. These relatively unreactive aldehydes and ketones permit further rearrangement of **1.10** to **1.11** resulting in the γ-coupled adduct.

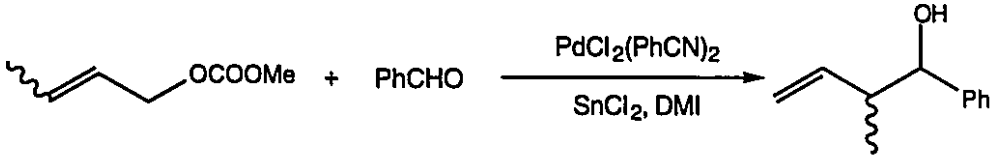
Carbonyl allylation by allylic acetates with Pd(0)/$SnCl_2$ occurs regio- and chemoselectivity to afford the corresponding homoallylic alcohols. The allylation of an aldehyde is chemoselectively performed in the presence of a ketone

group or an ester group; for example, the allylation of 10-oxo-undecanal provides 13-oxotetradec-1-en-4-ol in 68% yield (Scheme 1.14).[37]



Scheme 1.14

Allylic carbonates are more active than the corresponding acetates in carbonyl allylation using $PdCl_2(PhCN)_2/SnCl_2$,and the crotylation of benzaldehyde at 10°C exhibit slight anti selectivity (Scheme 1.15). Even allylic alcohols can be used for the $PdCl_2(PhCN)_2/SnCl_2$-mediated allylation. Diastereoselectivity in the allylation of benzaldehyde with E-but-2-en-1-ol is controlled by the choice of polar solvent although the selectivity achieved is not high; use of DMSO at 25°C leads to syn preference (at most 84:16), whereas anti preference is observed in THF at -10°C (90:10).[38]



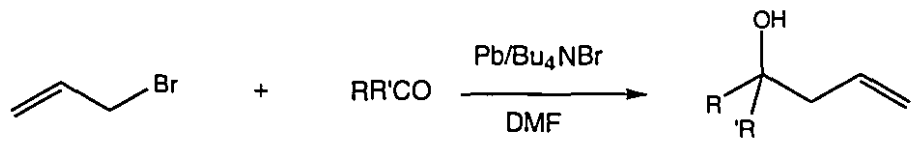
E or Z

from E carbonate syn : anti = 33:67
from Z carbonate syn : anti = 48:52

Scheme 1.15

The lead promoted allylation of carbonyl compounds with allyl bromide in $Pb/Bu_4NBr/Me_3SiCl/DMF$ systems has been performed in good yields with high chemoselectivity (Scheme 1.16).[39] An in situ method for preparing a reactive allyllead reagent is attractive from the standpoint of convenience since it avoids the need to isolate the organometallic reagent. In addition, catalytic systems

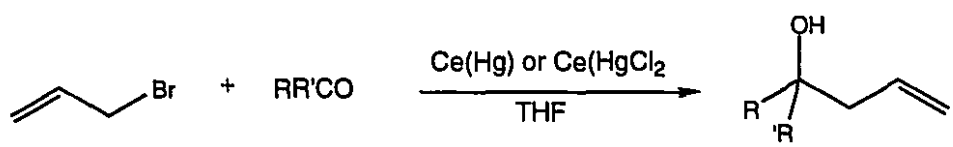
have been designed in which allylation of carbonyl compounds with allyl halides can be successfully performed by the action of a catalytic amount of $PbBr_2$ and Al foil in THF and DMF.[40]



Scheme 1.16

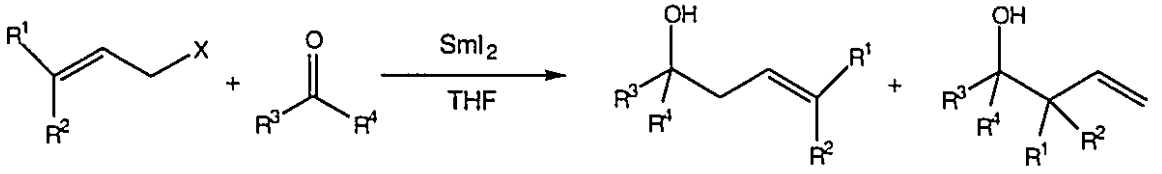
A. VI Allylic Lanthanoid Reagents (Ce, Sm).

Cerium amalgam Ce-(Hg) or Ce-($HgCl_2$) is an effective reagent for the chemoselective preparation of homoallyl alcohols from allyl halides and carbonyl compounds (Scheme 1.17).[41] The reaction of alkyl and phenyllithiums with CeI_3, prepared in situ by the reaction of Ce metal with iodine in THF, produces organocerium reagents. The reagents are less basic than organolithium and Grignards reagents, and they react cleanly at -78°C to -65°C with various carbonyl compounds to afford the addition products in high yield. These reagents react with α, β-unsaturated carbonyl compounds to yield 1,2-addition product in high regioselectivity.



Scheme 1.17

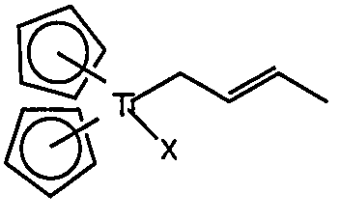
Another allylic lanthanoid reagent of interest is the allylic samarium reagent which when generated under Barbier-type conditions with SmI_2, produces homoallylic alcohols as a mixture of linear and branched isomer with the linear adduct predominating (Scheme 1.18).[42]



Scheme 1.18

A. VII Allylic Titanium and Zirconium Reagents

Allyl titanium and zirconium reagents react with carbonyl compounds to give the corresponding homoallylic alcohols in a highly regio- and stereoselective fashion. The impressive diastereo- and regiocontrol that can be achieved with achiral allyltitanium can be explained by a six-membered cyclic transition state with a chair conformation. For example, the crotyltitanium reagent **1.12** (X= Cl, Br. I) adds to aldehydes to give the γ-adduct with high anti stereoselectivity. Similar regio- and stereoselectivity were observed for the corresponding zirconium reagent.[43]



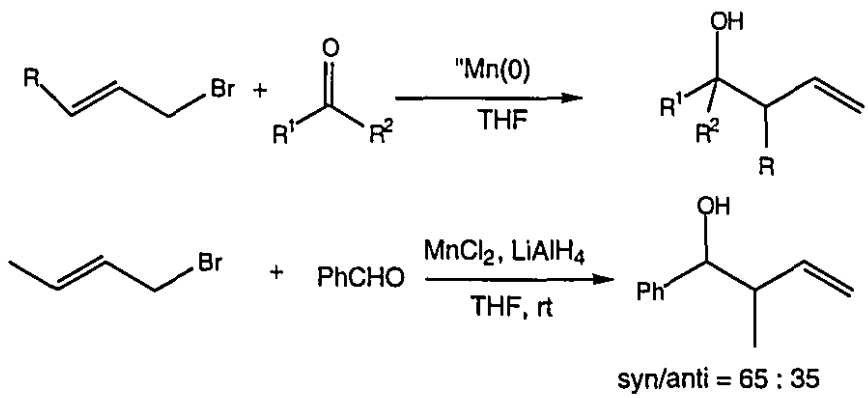
1.12

A. VIII Allylic Chromium Reagents

Allylic halides add to aldehydes in the presence of chromium (II) salts; $CrCl_2$ is generated in situ by the $LiAlH_4$ reduction of $CrCl_3$ in THF. The reaction is highly stereoselective and affords the γ-adduct with anti diastereoselectivity regardless of the geometry of the starting allylic halide.[44]

A. IX Allylic Manganese Reagents

Treatment of "Mn (0)" reagent, prepared in situ from anhydrous manganese (II) chloride and $LiAlH_4$ in THF at 0°C, with allylic bromide and then with aldehydes or ketones provides homoallylic alcohols with allylic rearrangement (Scheme 1.19).[45] α, β-Unsaturated aldehydes and ketones undergo 1,2-addition. With crotyl bromide, carbonyl addition produces a mixture of syn- and anti-isomers; the diastereoselectivity is low to moderate and normally, the syn-isomers are formed predominantly (Scheme 1.19).



Scheme 1.19

Allyl phosphate and chlorides can be used in place of the bromides. Metallic manganese powder suspended in THF containing iodine under reflux is also applicable to C-C bond formation including the Barbier-type allylic carbonyl addition.[46]

A. X Allylic Bismuth Reagents

In the presence of metallic bismuth (0), allyl bromide and iodide react with aliphatic and aromatic aldehydes in DMF at room temperature to give the homoallylic alcohols in good to excellent yields.[47]Acetophenone is not allylated

under these conditions. The allylation also proceeds smoothly by $BiCl_3$/Zn (0) in THF and $BiCl_3$/Fe (0) in THF at room temperature. The addition of crotyl bromide to benzaldehyde produces the syn adduct predominantly in many of the bismuth mediated procedures. However, the $BiCl_3$/Fe (0) procedure gives higher anti-selectivity.

1.2 Metal-mediated reactions in Aqueous Solvents

The development of carbon-carbon bond forming reactions that can be carried out in aqueous media is one of the most challenging task in organic synthesis. One such reaction which is of interest to organic chemist is the Barbier reaction: the reaction between a halogenated derivative and a ketone or an aldehyde in the presence of metal. As an organometallic intermediate species is often postulated, the reaction is usually conducted after careful exclusion of water. Yet it has been shown that this reaction takes place not only in the presence of some water, but even in water itself.

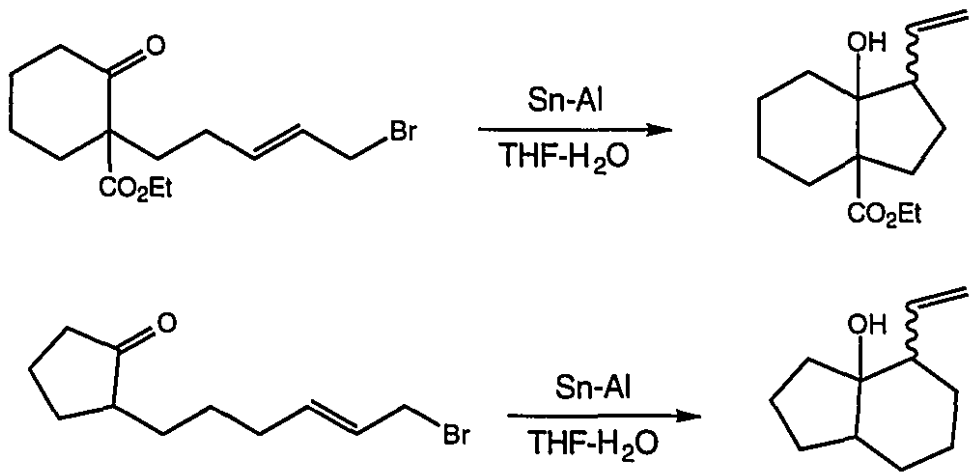
The utility of aqueous reactions is now generally recognized. For example, it is desirable to perform reactions of unprotected sugars or peptides in aqueous media because of their solubility. Compounds containing water of crystallization require tedious procedures to remove the water. These steps are not necessary if the reactions can be successfully carried out in aqueous media Moreover, aqueous reactions of organic compounds avoid the use of harmful organic solvents.

On the other hand, water often interfere with organic reactions. Although Lewis acids or organometallic reagents have played important roles in modern organic synthesis, even a small amount of water stops reactions using these reagents because the reagents immediately react with water rather than the substrate.

Despite the challenging nature of aqueous mediated organometallic reactions, there has been tremendous efforts and advances made in this field. The aqueous reactions studied include allylation of carbonyl compounds, Micheal type addition to α, β-unsaturated carbonyl compounds, crossed aldol Reformatsky-type reactions and pinacol-coupling reactions.

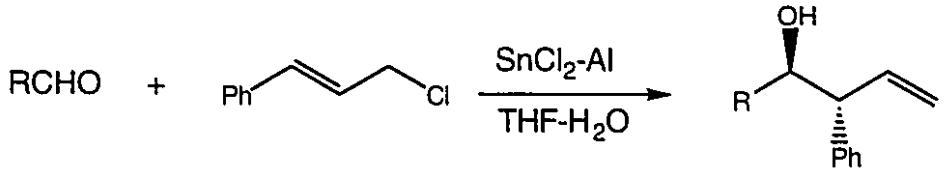
A. Allylations mediated by Zn, Sn and Bi in aqueous media

Allylations are by far the most successful Barbier-type reactions in aqueous media. The availability of a metal surface is critical in the success of these reactions. In 1977, the first allylation reaction involving aqueous media was carried out in 95% ethanol and butanol by using activated Zn dust.[48] However, only a moderate yield was obtained. In 1983, it was found that diallyltin dihalide-based allylation could be accelerated by the presence of water. The allylation of aldehydes and ketones by allylic bromides in the presence of water, metallic tin and aluminum[49] was applied to an intramolecular reaction to prepare 5- or 6-membered rings (Scheme 1.20).[50]



Scheme 1.20

The active zero-valent tin could be generated by $SnCl_2$/ Al in aqueous solvent providing excellent regio- and diastereoselection in the reaction of cinnamyl chlorides with aldehydes (Scheme 1.21).[51,52]

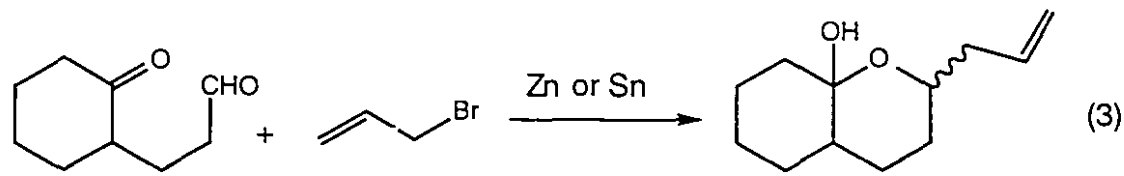


d.e. 96

Scheme 1.21

When treated with water-THF mixtures in the presence of $BiCl_3$/Al, allylic bromides react with aldehydes to afford the corresponding homoallylic alcohols in high yields. A similar reaction occurred with bismuth metal or bismuth (III) chloride together with Zn or Fe.[53]

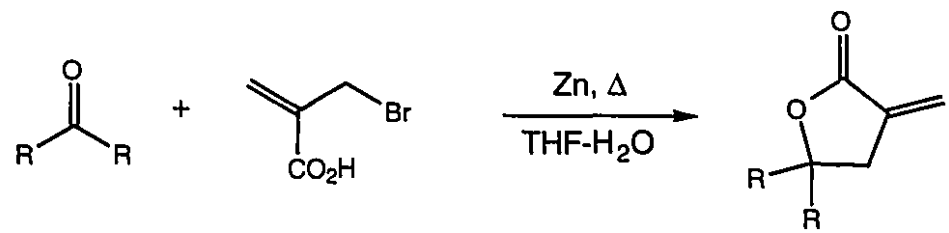
Allylic bromides or chlorides react with carbonyl compounds in water-THF mixtures also in the presence of Zn, with consistent improvement in yields due to the addition of either ammonium chloride[54] or C-18 silica as a solid organic support.[55] For example, the use of saturated aqueous NH_4Cl/THF solution instead of water/THF, dramatically increased the yields. Under the same conditions, metallic tin was also effective. When a mixture of aldehyde and ketone was subjected to these conditions, highly selective allylation of the aldehyde was achieved. Similar chemoselectivity occurred in compound **1.13** (Eq.3)



(3)

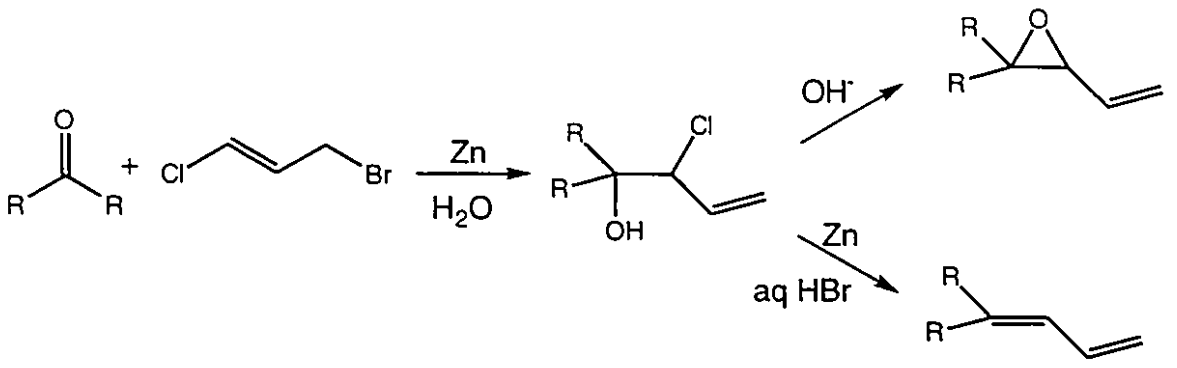
1.13 1.14

The use of ethyl 2-(bromomethyl) acrylate, instead of allyl halides, with zinc or tin in saturated aqueous NH_4Cl/THF under refluxing conditions followed by treatment with acid gave α-methylene-γ-butyrolactones.[56] The same products were obtained under much stronger conditions by refluxing 2-(bromomethyl) acrylic acid and carbonyl compounds with Sn-Al,[57] $SnCl_2$-AcOH,[58] $SnCl_2$-Amberlyst 15[59] in aqueous media (Scheme 1.22).



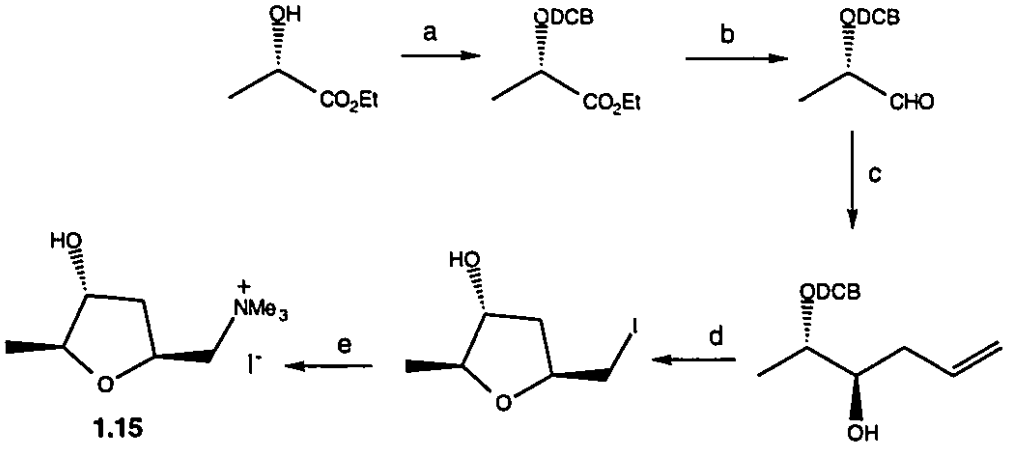
Scheme 1.22

Treating 1-chloro-3-iodopropene and aldehydes or ketones with zinc powder in aqueous medium led to the corresponding chlorohydrins which are convenient intermediates for the preparation of E-buta-1,3-dienes or vinyloxiranes (Scheme 1.23).[60]



Scheme 1.23

The zinc mediated aqueous methodology was applied to a concise synthesis of (+)-muscarine,**1.15** (Scheme 1.24).[61]



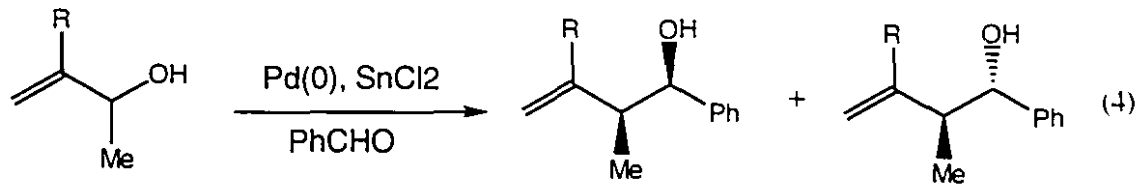
(a) DCBBr/Ag_2O/Et_2O/reflux/6h; (b) DIBAL-H/Et_2O/-78°C/2h; (c)CH_2=$CHCH_2Br$/Zn/H_2O/NH_4Cl/3h (d) I_2/CH_3CN/0°C/3h; (e) NMe_3/EtOH/80°C/4h.

Scheme 1.24

Luche found that allylation reactions, when subjected to ultrasonic radiation (sonication), could be performed with Zn metal.[54] Similarly, the same types of reactions using metallic tin, was improved using the same method.

The allylation of carbonyl compounds in aqueous media with $SnCl_2$ can also employ allylic alcohols[62] or carboxylates[63] in the presence of palladium catalyst. The diastereoselectivity of the reaction with substituted crotyl alcohols

was solvation dependant. Improved syn-diastereoselectivity was obtained with a mixture of water and THF or DMSO instead of using the organic solvent alone (Eq. 4).

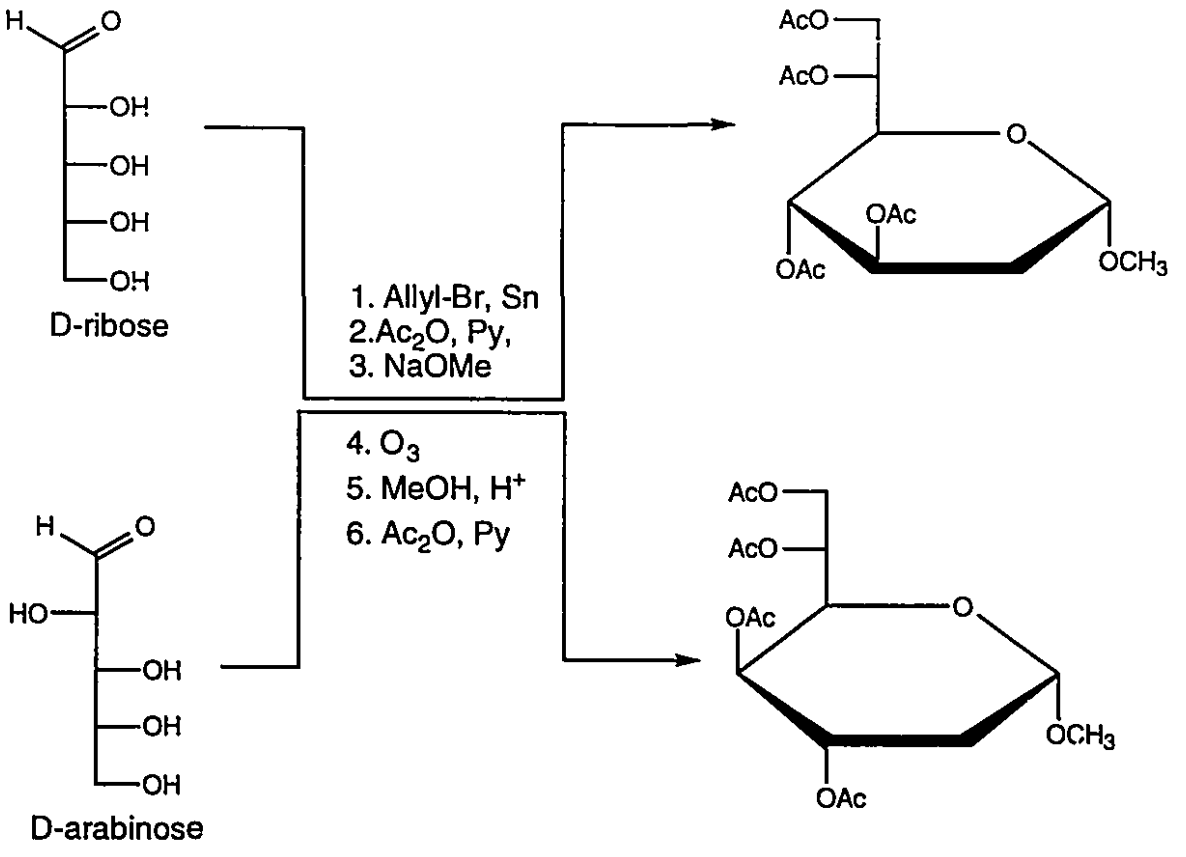


(4)

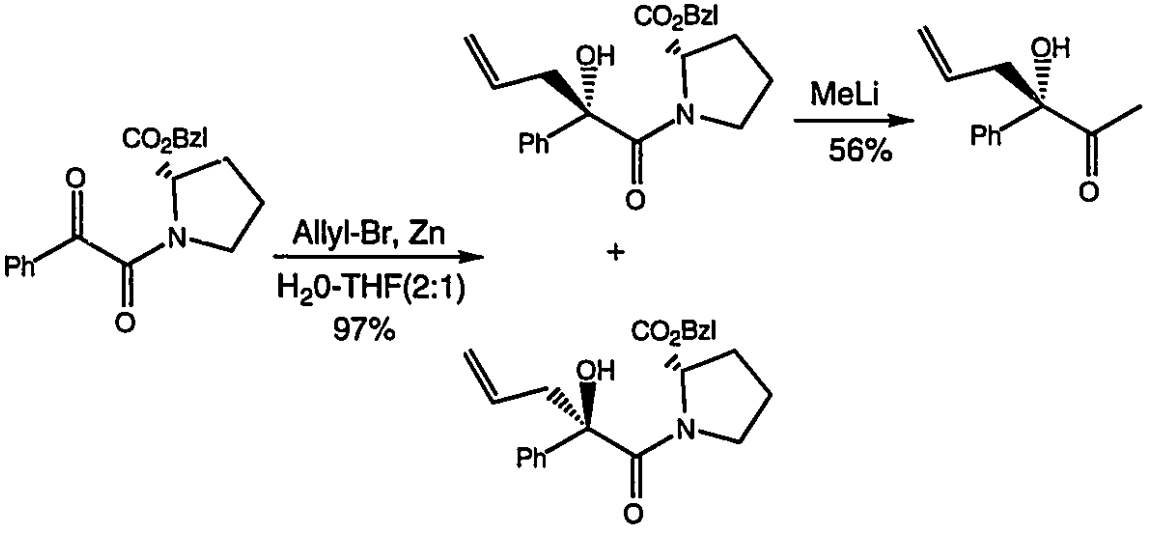
Allylations, allenylations and propargylations of carbonyl compounds in aqueous media could also be carried out using Bu_2RSnCl (R=allyl, allenyl or propargyl) as a mediator instead of the metallic tin.[64]

Whiteside et. al have applied the tin-mediated allylation to the carbonyl moieties of carbohydrates in aqueous/ organic solvent mixtures. The adducts were converted to higher carbohydrate homologues by subsequent ozonolysis and derivatization (Scheme 1.25).[65] The reaction showed higher diastereoselectivity when there was a hydroxyl group at C-2 (aldose numbering).

In an asymmetric Barbier-type reaction, α-keto amides of proline benzyl esters reacted with allylic bromides when treated with Zn, leading to the corresponding α-hydroxy amides in high yields and with good stereoselectivities (Scheme 1.26).[66]

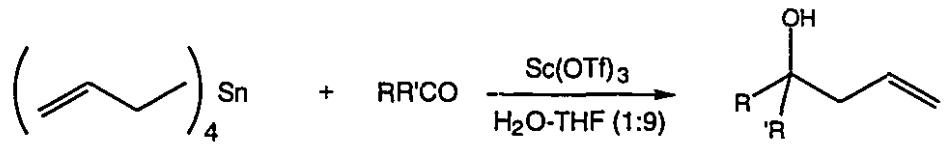


Scheme 1.25



Scheme 1.26

Recently, novel Lewis acids, lanthanide or scandium compounds, which can be used not only in organic solvents but also in aqueous media have been developed. Kobayashi et al. have demonstrated the aqueous allylation reactions of carbonyl compounds using scandium trifluoromethanesulfonate (Scandium triflate, $Sc(OTf)_3$) and tetraallyltin. The reactions proceeded smoothly in the presence of only catalytic amounts of $Sc(OTf)_3$ under extremely mild conditions giving the homoallylic alcohol in high yields (Scheme 1.27).[67]



Scheme 1.27

B. Aqueous allylations mediated by Indium. Why Indium?

The chemistry of indium resembles that of zinc and tin making possible a wide variety of useful organic transformation. Although the importance of indium has been almost entirely due to the significance of indium semiconductors, the synthetic potential of organoindium compounds was not appreciated until very recently. In contrast to organoboranes and organoaluminums, the preparative chemistry of organoindium compounds have received relatively little attention.

Some striking properties of this rare metal (natural occurrence is about 0.1 part per million) should be firstly pointed out. Indium is very soft, quite plastic and can be easily bent. The metal (m.p. 157°C) belongs to a series of low melting solid elements such as gallium, cadmium, tin, bismuth, or alkali metals. Furthermore, indium exhibit specific properties with profitable uses in synthesis. Indium metal is unaffected by air or oxygen at ordinary temperatures, but on

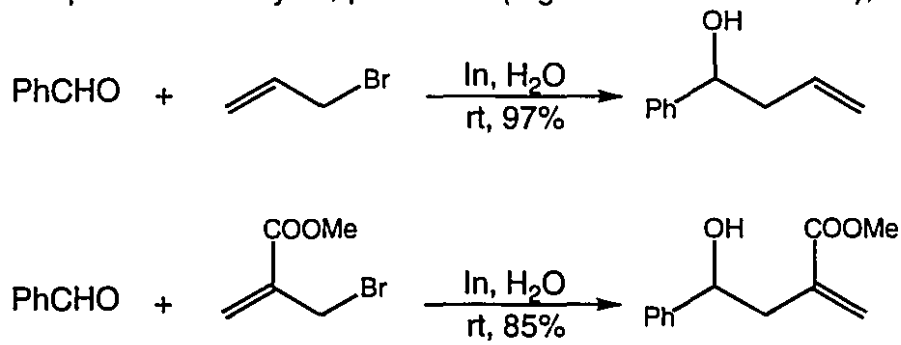
heating forms stable indium (III) oxide. Indium is practically unaffected by water and very resistant to alkaline conditions, although it dissolves in mineral acids.

Remarkably, the first ionization potential of indium (5.8 eV) is much lower than that of zinc (9.4 eV) or tin (7.3 eV), and even magnesium (7.6 eV), so that indium metal will be a suitable candidate in single electron transfer (SET) processes. Such a value is also lower than those of gallium and thallium, and closer to the first ionization potential of alkali metals like lithium or sodium (~5.0 eV). Thus, if it is suspected that metal-mediated reactions in aqueous media occur likely by a single electron transfer mechanism, reactions with indium should be readily conducted.

Indium exhibits, in general, a low heterophilicity in organic reactions where it is considered a suitable metal reagent to mediate carbon-carbon bond formation (see above). Thus oxygen and nitrogen containing functionalities are usually tolerated within the molecules whereas the well-known procedures involving zinc and tin readily generate the corresponding organometallic or enolate. Moreover, indium-assisted reactions display low nucleophilicity, a characteristic shared by a few organometallics, thus permitting chemoselective transformations at groups with similar reactivity.

Even though some indium mediated reactions are unprecedented in organic synthesis, the reactivity and selectivity of indium species in organic solvents are in many instances, comparable with those of zinc and tin. However, the recent development of an aqueous organometallic chemistry, assisted by elemental metals and water-tolerant organometallics, has turned considerable attention to indium in view of its exceptional stability to air and water. In fact, it is the organometallic reactions in an aqueous environment that illustrates the advantages of using indium chemistry.

Indium has been shown to effect allylation of aldehydes and ketones in water at room temperature and without inert atmosphere (Scheme 1.28).[68] Allyl bromide was found to be as good as allyl iodide in this reaction. Even the less reactive allyl chloride can be used, but the reaction requires longer reaction times and gives lower yields. Compared with other metals, particularly zinc or tin, which require acid catalysts, promoters (e.g. ammonium chloride), heat, or

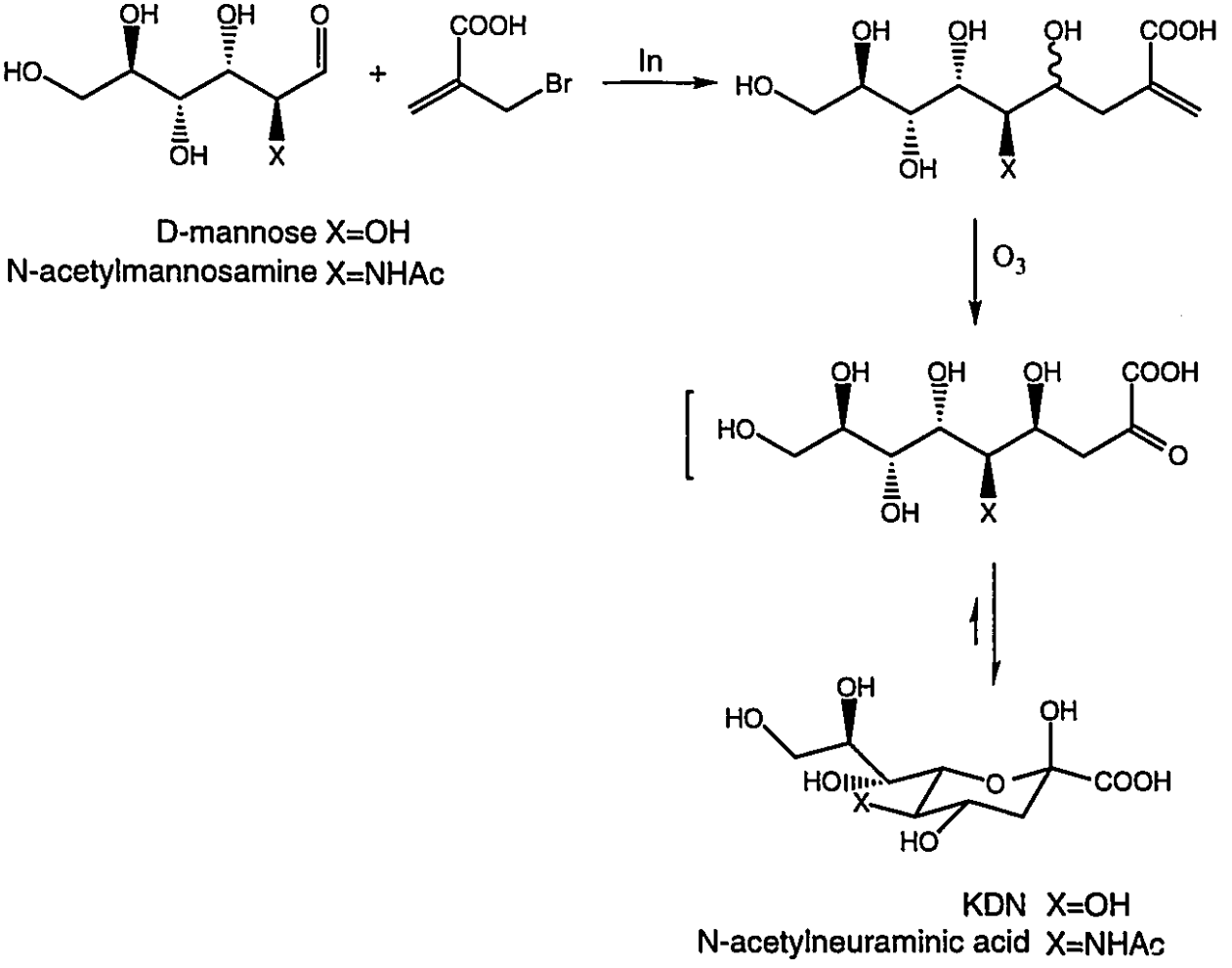


Scheme 1.28

sonication, reactions with indium are easily conducted at ambient temperature in higher yields and without the need for any promoter. Hydroxyl groups do not require protection and acid sensitive groups such as acetals remain unaffected during allylation. Moreover, side products resulting from Wurtz-type coupling or pinacol coupling, which are sometimes observed in zinc and tin mediated reactions, are absent with indium. The reaction has also been extended to bromomethylacrylate esters or the corresponding acids providing hydroxy acrylic esters or hydroxy acrylic acids, which are precursors to α-methylene-γ-lactones.[68,69] These processes occur very likely by SET processes on the indium metal surface rather than in solution.[70]

The compatibility of indium reagents with hydroxyl groups can be advantageously utilized with unprotected carbohydrates, substances insoluble in organic solvents. Unprotected aldoses such as D-arabinose, D-ribose and D-glucose react with allyl bromides in aqueous media, in the presence of

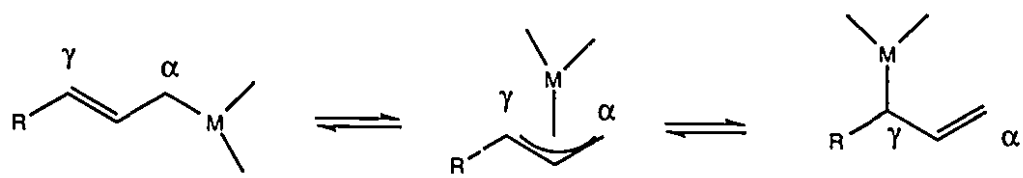
powdered indium metal, to give the corresponding homoallylic alcohols in good yields and with excellent diastereoselectivity.[71] In all the cases, the major product possesses a threo or syn relationship between the newly created hydroxyl group and the existing C-2 hydroxyl group of the starting carbohydrate. The aqueous indium-mediated reaction was interestingly used in the allylation of unprotected mannose and N-acetylmannosamine to afford 3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN) and N-acetylneuraminic acid (sialic acid) respectively (Scheme.1.29).[69]



Scheme 1.29

1.3 Factors Influencing the Regiochemistry of Metal-Mediated Allylations.

The metal-mediated coupling of carbonyl compounds with γ-substituted allylic halides usually present organic chemist with a problem of controlling the regiochemistry of the reaction. Provided that the substituted allylic halide generates the corresponding allylmetal intermediate, the carbonyl compound (the electrophile) may react at either of the termini (α- or γ-) of the allylmetal (**1.16**).



1.16a **1.16b** **1.16c**

A great deal of effort has been exerted to control the regioselectivity (α : γ ratio); regioselective attack at the γ-position of the allylmetal leads to the branched homoallylic alcohol, whereas the attack of the α-position leads to the corresponding linear alcohol. This α/γ-selectivity is dictated by a number of factors, such as the nature of the metal, the type of electrophile, additives and solvents, substituents attached to allylic unit, reaction temperature, and reaction time (as shown above). Predicting the regioselectivity in the reaction of an allyl anion equivalent like **1.16** with an electrophile is of fundamental importance to organic chemistry. One particular theoretical approach toward predicting the regiochemical outcome of the allylic anion coupling is the Frontier Molecular Orbital theory (FMO).

The qualitative description of reactivity in molecular orbital terms begins with a basic understanding of the molecular orbitals of the reacting system. The reacting system of interest is the allylic anion. The subsequent theoretical

analysis considers how structural changes (perturbations) in the allylic unit affects the molecular orbital patterns. The type of changes which can be handled in a qualitative way are substitution of atoms by other elements or groups with a resulting change in electronic distribution.

As molecules approach one another and the reaction proceeds, there is a mutual perturbation of the molecular orbitals. This process continues until the reaction is complete and the new products are formed. The FMO theory proposes that during such a process, the most important interactions will be between a particular pair of orbitals.[72] These orbitals are the highest filled molecular orbital (the HOMO, highest occupied molecular orbital) of one reactant and the lowest unfilled orbital (the LUMO, lowest unoccupied molecular orbital) of the other reactant. The basis of concentrating on these two molecular orbitals is that they will usually be the closest in energy of the interacting orbitals. The basic postulate of the theory is that the strongest interactions are between orbitals that are closest in energy and that these strong initial interactions can then guide the course of reaction as it proceeds to completion.

In general, the important frontier orbitals for a nucleophile such as the allylic anion reacting with an electrophile are HOMO (nucleophile)/ LUMO (electrophile) Fig 1.1.

Having identified the theoretical aspects of FMO as it applies to the ease of reactivity, the factors influencing the site-selectivity of the allylic anion will be considered. For the allyl anion, molecular orbital calculation shows that the overall excess of electron density is concentrated on C-1(Cα) and C-3 (Cγ), and it is therefore at these sites that charged electrophiles will attack. In molecular orbital terms, the HOMO of the anion has coefficients at C-1 and C-3 of $\pm$ 0.707. The coefficient on C-2 is zero (Fig. 1.2).

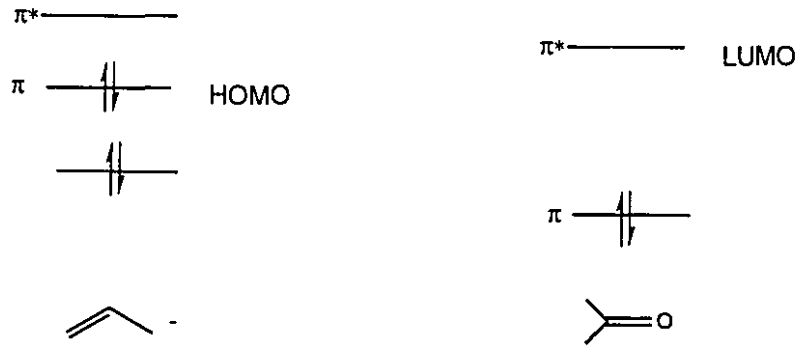


Fig. 1.1 Relative energies of the HOMO of the allyl anion and the corresponding carbonyl electrophile

When the substituent R on the allylic unit **1.16** is an anion- destabilizing substituent (electron-donating groups), higher electron density, and therefore a larger molecular orbital coefficient, would be expected at the α-position and **1.16a** would be preferred over **1.16c**. Accordingly, alkyl halides and protons would react at the α-position (the site of higher electron density), while carbonyl compounds would react at the γ-position via a rearrangement process involving the metal. When R is an anion-stabilizing substituent (electron-withdrawing groups), **1.16c** would be preferred over **1.16a** and thus complementary regioselectivity would be observed. In fact, allylic anions, substituted by anion-destabilizing groups such as OR, NR_2 and alkyl, undergo alkylation and protonation preferentially at the α-position and react with carbonyl compounds predominantly at the γ-position. Allylic anions bearing anion stabilizing groups (Y= SR, BR2) react with carbonyl compounds at the α-position and with alkyl halides and protons at the γ-position.

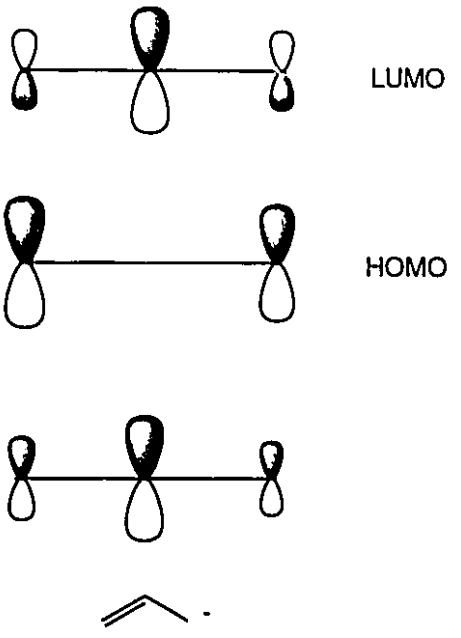


Fig. 1.2 π-Molecular orbitals of the allylic anion

However, these tendencies may be modified by a number of factors as mentioned above. Nevertheless, the FMO theory will continue to be useful as a starting point towards predicting regiochemistry prior to the experimental observation.

1.4 Proposed Research

Many approaches to the stereoselective C-C bond formation via the reaction of allylic metals with carbonyl electrophiles have been investigated. A variety of very successful methods have been developed for diastereoselective C-C bond formation between allylic metals and carbonyl compounds in organic solvent. In addition, the diversity and potential usefulness of carrying out organic reactions in aqueous media has also been demonstrated. Particularly interesting is the use of indium metal as a mediator for the allylation of carbonyl compounds in water as solvent. The exact role of water in these reaction is not yet well understood. Nevertheless, the advantages of using water as solvent for organic reactions are numerous. An aqueous medium is very economical and it

avoids the use of inflammable organic solvents. Protection-deprotection processes, product isolation, and catalyst recycling can sometimes be simplified.

In spite of the recent use of indium metal in simple allylations in organic and aqueous solvents, the aforementioned regio-, stereo- and chemoselective aspects of these reactions, using γ-substituted allylic units in water have not been investigated. Also unprecedented in the literature is the role of indium as a mediator in the reaction of propargyl systems with carbonyl compounds in water.

It is therefore our intention to investigate these aspects of the indium-mediated methodology along with its application to the synthesis of novel functionalized carbohydrates.

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Chapter 2

Indium-Mediated Coupling of Aldehydes with γ-Functionalized Allyl Bromides in Aqueous Media. Investigation of the Factors Governing Regio-, Chemo- and Diastereoselectivity.

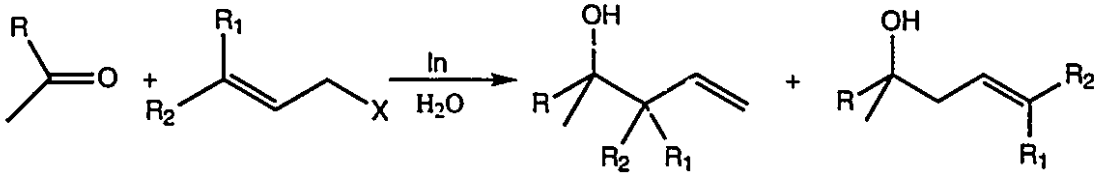
For several decades, the regio-, chemo and stereoselective aspects of carbon-carbon bond construction, have been an area of critical importance in organic synthesis. Carbon-Carbon bond forming reactions are such that one may very crudely distinguish between competing reaction types (*typoselectivity* or *chemoselectivity*), reaction sites (*regioselectivity* or *positional selectivity*) and topomorphologies (*stereoselectivity*).[1]

One of the most challenging problems for the synthetic organic chemists today is the control of stereochemistry in conformationally nonrigid open-chain compounds. There is hardly a single recent report of natural product synthesis in which stereoselectivity is not claimed in the title. Often it is not enantioselectivity, but rather diastereoselectivity that poses the more difficult problem. The quest for generally applicable principles to the understanding of stereoselectivity has almost certainly not ended despite the wealth of information to be found in a number of very useful reviews and books.[2]

The reaction of allylic organometallic reagents with aldehydes constitutes a useful procedure for controlling the stereochemistry in acyclic systems (see Chapter 1). This allylmetal-aldehyde addition has proven to be one of the most synthetically useful method of carbon-carbon bond formation.[3] The utility of this reaction derives from the high yield, excellent regio- and stereoselectivity, and mild conditions under which the reactions can be performed. When the allyl metal is substituted at the γ-terminus, four isomers (two enantiomeric pairs of syn and anti diastereomers) can be formed. The syn/anti selection process is

often determined by the preferred orientation of the reactive double bond in the transition structure.

Recently, indium has been found[4] to be the metal of choice to mediate the coupling of allyl halides with carbonyl compounds in aqueous media. The reaction has been applied to the synthesis of 3-deoxy-D-*manno*-2-octosulonic acid (KDO),[5] 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN),[6] and N-acetylneuraminic acid.[7]



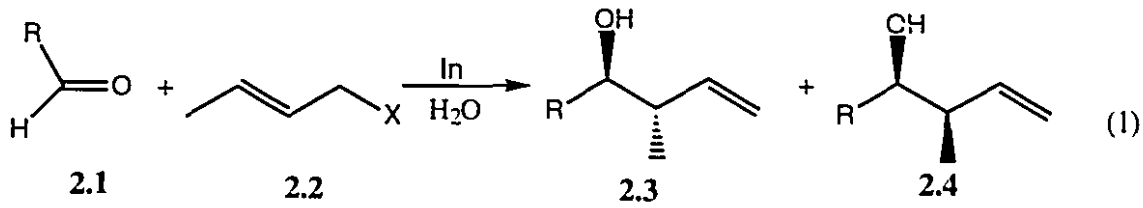
Scheme 2.1

In spite of the application of indium mediated reactions in aqueous media to organic synthesis, little is known about the regio-and diastereoselectivity of these reactions (Scheme 2.1). It is therefore our goal to investigate these aspects of the indium mediated reactions in water.

2.1 Regio-and diastereoselectivity of Indium mediated reactions in water

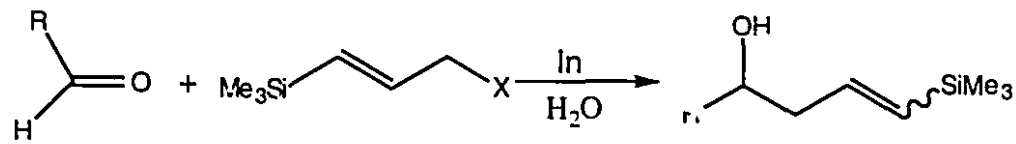
The only information available prior to this study was the report by Whitesides *et. al* [8] who found that in the coupling of aldehyde **2.1** with crotyl bromide (**2.2**) mediated by indium in water (equation 1), the reaction was γ–regioselective but poorly diastereoselective giving a mixture of anti (**2.3**) and syn (**2.4**) isomer. On the other hand, we found that for the coupling of the same aldehyde **2.1** with 1-trimethylsilylpropenylbromide (**2.5**), the reaction was α–regioselective in giving a mixture of E- and Z-vinylsilanes **2.6** (equation 2). It is

clear that if the reaction is to find further application in synthesis, we must gain a better understanding of the origin of regio- and diastereo-selectivity.



(1)

2.1 **2.2** **2.3** **2.4**

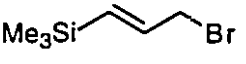
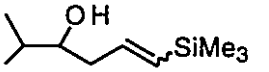
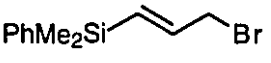
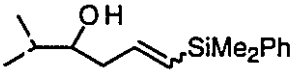
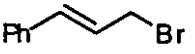
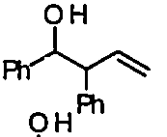
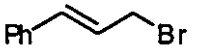
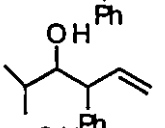
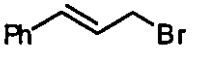
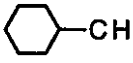
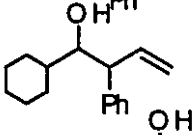
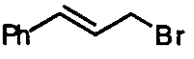
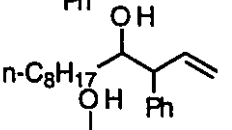
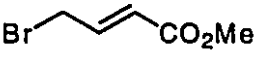
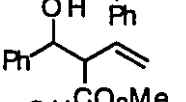
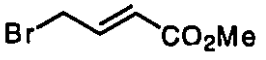
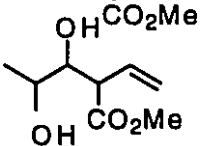
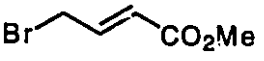
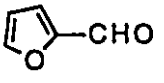
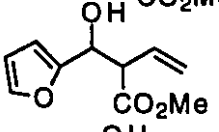
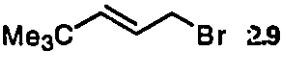
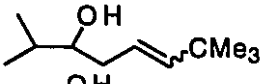
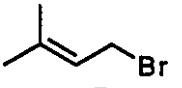
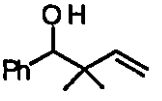
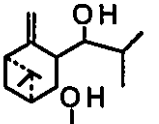
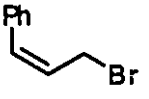
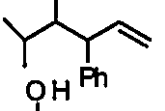
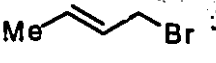
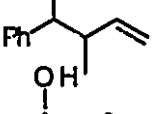
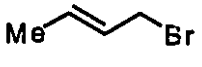
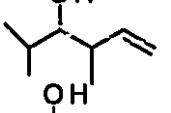
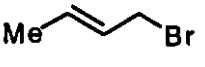
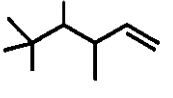


(2)

2.1 **2.5** **2.6**

A number of γ-substituted allyl bromides were prepared and their reactions examined with aldehydes under aqueous media mediated by indium. The results are summarized in Table 2.1. In all cases, good yields of the coupling product were obtained.The following conclusions can be drawn. (1) Regioselectivity is not governed by the conjugation of the double bond with the γ–substituent. This is clear from the observation that whereas **2.5** or **2.7** gave the α–regioisomers **2.6** (entries 1 and 2), E-cinnamyl bromide (entries 3-6) or methyl 4-bromo-E-crotonate (**2.8**, entries 7-9) gave the de-conjugated adducts. (2) Regioselectivity appears to be governed by the steric size of the γ–substituent, but not by the degree of substitution. This is based on the observation that t-butyl substituted allyl bromide **2.9** coupled with aldehyde (entry 10) to give the corresponding α–regioisomers, similar to the silyl substituents in **2.5** and **2.7**. On the other hand, γ,γ-dimethylallyl bromide (**2.10**,entry 11) or the pinenyl bromide **2.11** (entry 12) reacted with aldehydes to give

TABLE 2.1: INDIUM MEDIATED ALLYLATION OF CARBONYL COMPOUNDS IN WATER

ENTRY	ALLYL BROMIDE	ALDEHYDES	PRODUCT	YIELD(%)
1	 2.5	$Me_2CH-CHO$		62 (E: Z =75 : 25)
2	 2.7	$Me_2CH-CHO$		50 (E: Z =68 : 32)
3		PhCHO		88(anti: syn=96:4)
4		$Me_2CH-CHO$		88(anti: syn=96:4)
5				75(anti: syn=90:10)
6		$n\text{-}C_8H_{17}-CHO$		80(anti: syn=69:31)
7	 2.8	PhCHO		75(anti: syn=84:16)
8		$Me_2CH-CHO$		81(anti: syn=92:8)
9				88(anti: syn=72:28)
10	 2.9	$Me_2CH-CHO$		87 (E: Z =80 : 20)
11		PhCHO		90
12	 2.10	$Me_2CH-CHO$		86(one isomer)
13		$Me_2CH-CHO$		79(anti: syn=90:10)
14	 2.11	PhCHO		92(anti: syn=50:50)
15		$Me_2CH-CHO$		88(anti: syn=84:16)
16		Me_3C-CHO		87(anti: syn=80:20)

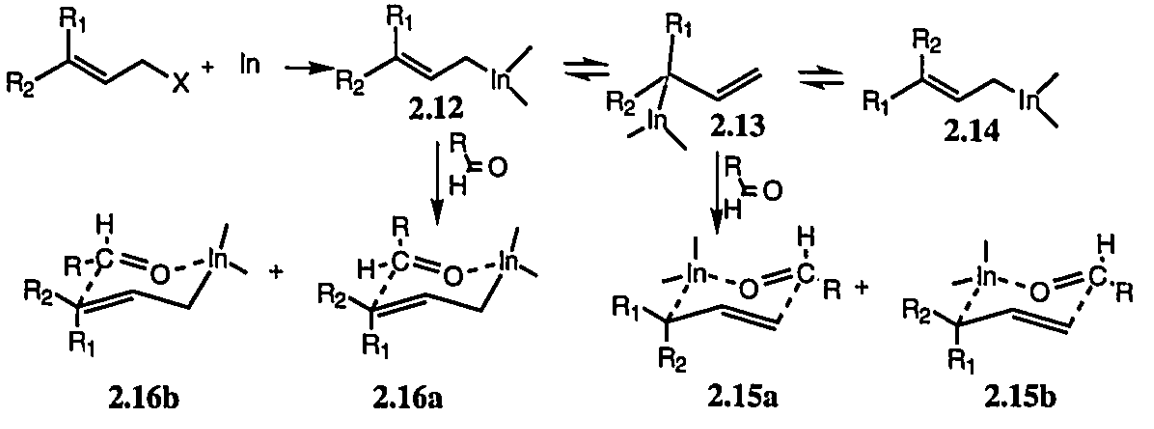
All reactions were carried out at room temperature using the aldehyde (1mmol), allyl bromide (2mmol), In (2mmol) in H_2O (2ml) . Isolated yields are reported and selectivities were determined from crude ^1H NMR.

the γ–regio adducts in spite of the high degree of substitution at the double bond. (3) In γ–regioselective coupling leading to a mixture of syn- and anti-diastereomers, the diastereoselectivity is governed by the steric size of the substituent of the aldehyde to give mainly the anti-isomer.[9] This is clear by comparing the series of different aldehydes reacting with the same allylic bromide. For example, of the three aliphatic aldehydes reacting with E-cinnamyl bromide (entries 4-6), diastereoselectivity improved as the size of the aldehyde increased from n-octyl to cyclohexyl to iso-propyl. (4) The diastereoselectivity appears to be independent of the stereochemistry of the double bond in the allyl bromide moiety. This is evident from the observation that Z-cinnamyl bromide coupled with iso-butylaldehyde (entry 13) to give nearly the same ratio of anti-/syn-isomers as the coupling of E-cinnamyl bromide with iso-butylaldehyde (entry 5). The possibility that the Z-cinnamyl bromide may have isomerized to the E-cinnamyl bromide first before coupling was ruled out since Z-cinnamyl bromide could be recovered unchanged if the reaction was allowed to proceed to half completion.

The reactions of ketones such as acetophenone and pentan-2-one failed to react under these reaction conditions. The ketones were recovered unchanged and some of the organic halide was transformed. The mere fact that ketones were recovered unchanged would seem to suggest that the organometallic species reacted with water than with the carbonyl substrate in these cases, because of the steric hindrance inherent in these molecules.

To account for the above observations, we propose in broad terms the following mechanism for the indium mediated coupling of allylic bromides with aldehydes in aqueous media (Scheme 2.2). First, an allyl indium species **2.12** is formed which exists in equilibrium with its regioisomer **2.13**. Because of this equilibrium, stereochemistry of the double bond in the allylic indium species

can be isomerized to favour the more stable E-isomer over the Z-isomer **2.14**. In the coupling with aldehyde, the reaction proceeds through several possible cyclic transition states, all with the carbonyl oxygen coordinated with indium. In cases where the γ–substituent in the allyl bromide is bulky (e. g. silyl or t-butyl), the cyclic transition states **2.15a** and **2.15b** are the preferred pathway giving rise to the mixture of α–adducts. In the other cases, the cyclic transition states **2.16** are favoured, and the diastereoselectivity is governed by the steric size of the substituent on aldehyde in differentiating between **2.16a** versus **2.16b**. Finally, in the pinenyl system (entry 12), the facial selectivity is governed by steric effect.



Scheme 2.2

The indium mediated coupling of aldehydes with γ–substituted allyl bromides can therefore proceed regio- and diastereoselectively. The factors governing the selectivity can now be understood and applied to the synthesis of complex molecules.

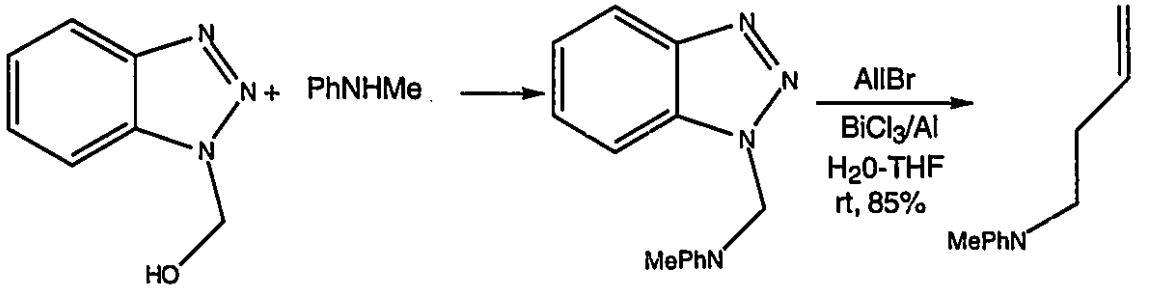
The previous discussion of the regio- and diastereoselective aspects of the indium-mediated couplings in aqueous media is indicative of the variations permitted in the allylic theme. This highlights one of the advantages of aqueous indium chemistry over that of other metals (particularly Zn and Sn) in that oxygen and nitrogen containing functional groups are usually tolerated.

Moreover, indium-assisted reactions display a low nucleophilicity, a characteristic shared by a few organometallics, thus permitting chemoselective transformations at groups of similar reactivity. For example, some organometallics such as organomagnesium and organolithiums display very high nucleophilicity and therefore lacks the ability to differentiate effectively between carbonyl function of an aldehyde and a ketone. Despite the remarkable chemoselective behavior demonstrated by indium in aqueous media, it is not without shortcomings. Reactions with indium, unlike zinc and tin, do not require an induction period which usually involves the use of acids for initiating the reaction. In addition, reactions of zinc and tin are often accompanied by reductive side products such as alcohols due to reduction of the carbonyl compounds, or pinacols due to reductive coupling. The use of indium has to a certain extent, circumvented some of these difficulties. It is nevertheless an expensive metal. Also, it was capable of reducing other functional groups A case in point is the coupling of p-nitrobenzaldehyde with allyl bromide. In all cases, irrespective of the metal (In, Zn or Sn), no coupling product could be obtained. Instead, the reaction mixture turned orange and the product obtained was not the desired homoallylic alcohol but appeared to be polymeric in nature. This difficulty was attributed to the susceptibility of the nitro group to the reductive conditions of these Barbier-type reactions.

2.2 Chemoselective Allylation of carbonyl compounds with Bismuth in Water.

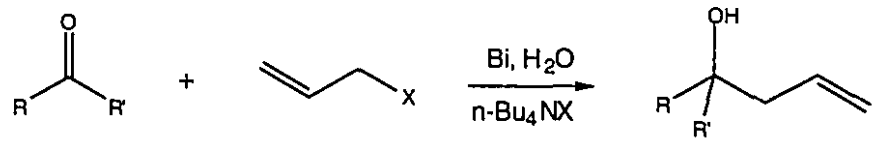
Despite the numerous metals available, only zinc, indium and tin have recently been suggested to be suitable mediators for the coupling of allylic halides with carbonyl compounds in aqueous media. However, all three metals show poor carbonyl selectivity towards nitro-functionalized carbonyl compounds. This poor result has been attributed to the tendency of the metals to reduce the nitro-function than to serve as a mediator for the carbon-carbon coupling reaction. In an attempt to overcome this limitation, we embarked on a search for a metal with attenuated reduction potential and at the same time, was an effective mediator for the coupling reaction in water as solvent. Bismuth, a cheaper and less toxic metal, was found to be ideal.

Recently, bismuth metal or $BiCl_3$ in combination with Zn, or Fe or Al were found to mediate the allylation of carbonyl compounds. However, in most cases, organic solvents (DMF or THF) were required as the reaction media.[10] Nonetheless, when treated with $BiCl_3$ / Al in water-THF mixtures, allylic bromides react with aldehydes to afford the corresponding homoallylic alcohol in high yields. Allyl chlorides and bromides were also found to react with N-(alkylamino) benzotriazoles in the presence of $BiCl_3$ / Al in a water-THF mixture to provide high yields of the homoalkylated amine (Scheme 2.3).[11]



Scheme 2.3

We have found that bismuth mediated the coupling of allyl halides with aldehydes in water to give the corresponding homoallylic alcohol in good yields (Scheme 2.4 and Table 2.2) provided that tetra-n-butylammonium halide was present as well.

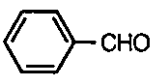
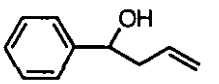
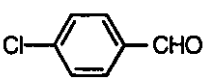
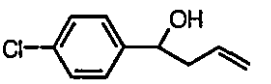
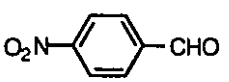
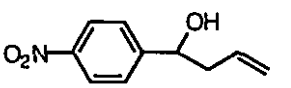
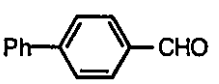
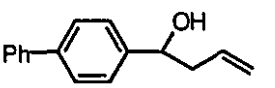
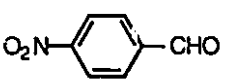
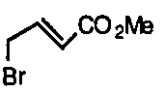
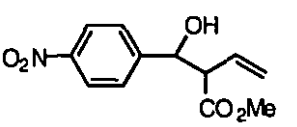
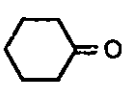
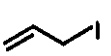
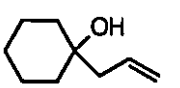
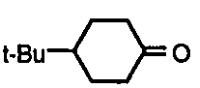
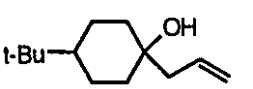
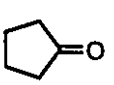
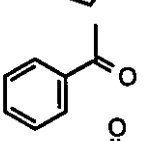
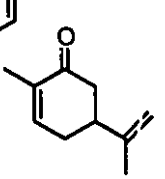
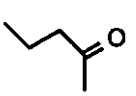
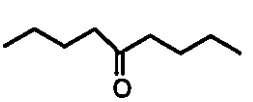
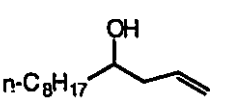


Scheme 2.4

When the bismuth metal alone was used (entry 1, Table 2.2), the reaction gave in general only about 50% yield of the desired products in spite of the use of excess metal or longer reaction times. However, in the presence of tetra-n-butyl ammonium halides (n-Bu4NX, X= Cl or Br), the reactions were practically complete in shorter reaction times with dramatically improved yields. The tetra-n-butylammonium salt presumably functioned as a phase transfer catalyst in the heterogeneous reaction mixture (Scheme 2.4).

Bismuth showed remarkable chemoselectivity in comparison to the other metals used hitherto for coupling reaction. This is evident from the fact that the nitro group is unaffected under the prescribed reaction conditions. Furthermore, p-nitrobenzaldehyde was coupled to methyl 4-bromobut-2-enoate under similar reaction conditions to give regioselectivity the γ-adduct with a syn : anti ratio of 12 : 88 (entry 7). Another feature of the chemoselectivity is that under the same conditions used for aldehydes, a range of ketones (aryl, alkyl and

TABLE 2.2: BISMUTH MEDIATED ALLYLATION OF CARBONYL COMPOUNDS IN WATER

ENTRY	CARBONYL COMPOUNDS	ALLYL HALIDE	n-Bu_4NX	REACTION TIME	PRODUCT	YIELD (%)
1			—	8		50
2	"	"	n-Bu_4NBr	8	"	89
3	"	"	n-Bu_4NCl	8	"	90
4		"	n-Bu_4NBr	8		94
5		"	"	8		90
6		"	"	8		60
7			"	8		80
8			"	16		35
9		"	"	16		40
10		"	"	24	—	0
11		"	"	24	—	0
12		"	"	24	—	0
13		"	"	24	—	0
14		"	"	24	—	0
15	n-C_8H_{17}CHO	"	"	8		71

cycloalkyl) could be recovered unchanged. With cyclohexanones (in longer reaction times than with aldehydes), the homoallylic alcohols were obtained in modest yields. When a mixture of equivalent amounts of benzaldehyde and acetophenone was subjected to a mixture of allyl iodide, bismuth, and tetra-n-butylammoniumbromide in water, only benzaldehyde was reacted to give the expected homoallylic alcohol in 95% yield. The unreacted acetophenone was recovered

quantitatively. Similarly, for a mixture of n-nonanal and 4-t-butylcyclohexanone, only the aldehyde was converted to the corresponding homoallylic alcohol in 82% yield.

2.3 Conclusion

It is clear that the facile aqueous indium mediated coupling of carbonyl compounds with γ-substituted allylic halides is not only high yielding, but also highly regio- and diastereoselective. The factors influencing selectivities can now be understood and applied to the total synthesis of complex natural products. In addition, the use of bismuth metal as an effective mediator in aqueous media when problems of chemoselectivity arise with indium metal is also highlighted. Further developments of the metal-mediated methodology in an aqueous environment will continue to be a crucial cornerstone for the preparation of both natural and unnatural products. The potential of this methodology is likely to have far-reaching implications in the industrial and synthetic community.

Experimental

General: Chemicals were purchased from Aldrich and were reagent grade. Analytical thin layer chromatography was performed on silica gel 60 F_{254} plastic back 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 (10 ml / 90 ml) and heated with a heat gun.

The Nuclear Magnetic Resonance spectra were recorded on a VARIAN Gemini 200 (^1H 500 MHz, ^{13}C 50 MHz) or a Unity 500 MHz (^1H 200 MHz, ^{13}C 125 MHz) spectrometer and chemical shifts are reported on the δ scales in parts per million (ppm) with solvent residue as references. Singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) were recorded at the centre of the peaks and were used throughout. IR spectra were recorded on an Analet FT A25-18 spectrometer between NaCl plates. Mass spectra were recorded on a Kratos MS25RFA mass spectrometer. Melting points were determined on a Gallenkamp block and were uncorrected.

General procedure for the coupling of the γ-substituted allylic bromide to aromatic and aliphatic Aldehydes: To a solution of the aldehyde (1 mmol) and the γ-substituted allylic bromide (2 mmol) in 2ml of H_2O , was slowly added indium powder(150 mesh, 2 mmol). The reaction mixture was vigorously stirred at room temperature for 3-4 hrs. The product mixture was extracted with ether and the separated organic layer washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography (hexane: ethyl acetate 20:1).

1-Isopropyl-2-phenyl-3-buten-1-ol: Colourless oil; (anti-isomer) ^{1}H nmr ($CDCl_3$) δ 0.94 (6H), 1.56 (m, 1H, Me_2CH), 1.73 (s, 1H, -OH), 3.40 (t, 1H, J= 8.33 Hz, PhCH), 3.61 (dd, 1H, J=4.28 and 8.33 Hz, CH-OH), 5.21 (m, 2H, $=CH_2$), 6.15 (m, 1H, CH=), 7.30 (5H, ArH); ^{13}C nmr ($CDCl_3$) δ 16.35, 20.87, 30.16, 54.97, 77.65, 117.16, 125.98, 127.29, 128.12, 138.01, 142.00; IR (neat) 3346, 1646, 1031, 849, 631 cm^{-1}; MS CI (NH_3) m/z 242 (M + NH_4, 1.6), 224 (M, 15.2), 207 (66.8),129 (31.2), 118 (100.0).[12]

Synthesis of the 1,3 acetonide[9] ***II*** *from 1-Isopropyl-2-phenyl-3-buten-1-ol*:

Through a methanolic solution of 1-isopropyl-2-phenyl-3-buten-1-ol (11.2 mg, 0.05 mmol), was bubbled O_3 gas for 90 minutes. The solution was degassed with argon and an excess of $NaBH_4$ (4 eq) was added. The mixture was stirred overnight. The solution was then poured onto dilute HCl and extracted with ether. The organic layer was separated, washed with brine and dried ($MgSO_4$). The resulting solution was concentrated in vacuo. To the crude 1,3-diol (11.2 mg, 0.05 mmol) obtained was added DMP (2ml) and catalytic amount of Ts-OH and the reaction mixture was stirred for 24 hrs. The solvent was removed in vacuo and the residue dissolved in minimum amount of hexane and purified by flash column chromatography through basic alumina. The acetonide was isolated in 87% (11.7 mg).^{1}H nmr ($CDCl_3$) δ 0.94 (6H), 1.44 (s, 3H) 1.50 (m, 1H, Me_2CH), 1.56 (s, 3H), 2.93 (td, 1H, J= 5.37 and 11.23 Hz, PhCH), 3.89 (dd, 1H, J= 5.37 and 11.23 Hz), 3.94 (t, 1H, J= 11.23 Hz), 3.95 (t, 1H, j= 11.23 Hz), 7.30 (5H, ArH); ^{13}C nmr ($CDCl_3$) δ 14.86, 19.33, 19.76, 28.97, 29.57, 44.43, 65.90, 76.88, 98.23, 126.94, 128.21, 128.67, 139.33.[9]

Synthesis of the syn-isomer 2.18

To a solution of **2.17** (20 mg, 0.09 mmol) in methylene chloride 5 ml was added PCC (1.5 eq). and the reaction mixture was stirred for 2hrs. The crude mixture was filtered through celite and the filtrate concentrated in vacuo. The crude ketone product was taken up into 5ml of methanol and subsequently treated with $NaBH_4$ (3 eq). The mixture was then stirred for 45 minutes. The solution was then poured onto dilute HCl and extracted with ether. The organic layer was separated, washed with brine and dried (Na_2SO_4). The resulting solution was concentrated in vacuo. ^1H nmr analysis of the crude product (relatively pure by nmr standards) compared well with the same compound isolated by Coxon et al.[12]

1,2- Diphenyl-3-buten-1-ol (anti-isomer) ^1H nmr ($CDCl_3$) δ 2.31 (d, 1H, J=2.56 Hz, -OH), 3.56 (t,1H, J=8.30 Hz, PhCH), 4.85 (dd, 1H, J= 2.56 Hz, J= 8.30 Hz, CH-OH), 5.24 (m, 2H, $=CH_2$), 6.26 (m, 1H, CH=), 7.25 (10H, ArH); ^{13}C nmr (CDCl3) δ 59.46, 77.21, 117.97, 126.07, 126.83, 127.31, 127.53, 127.59, 127.70, 137.11, 139.84, 141.02; IR (neat) 3332, 1607, 1074, 1418, 671 cm^{-1}; MS CI (NH_3) m/z 208 (M + NH_4, 58.5), 190 (M, 1.7), 173 (5.4), 118 (100.0).[12]

1-Cyclohexyl-2-phenyl-3-buten-1-ol Colourless oil; (anti-isomer) ^1H nmr ($CDCl_3$) δ 0.80- 2.00 (11H, cyclohexyl), 3.46 (dd, J=7.32 and J=8.79 Hz 1H, PhCH), 3.58 (dd, 1H, J=7.32 Hz CH-OH), 5.20 (m, 2H, $=CH_2$), 6.15 (m, 1H, CH=), 7.30 (5H, ArH). ^{13}C nmr ($CDCl_3$) δ 26.57, 26.92, 27.03, 27.10, 30.72, 53.93, 78.04, 117.18, 125.90, 127, 30, 128.06, 137.64, 141.26; IR (neat) 3305, 1637, 1417, 1037, 892 cm^{-1}; MS CI (NH_3) m/z 248 (M + NH_4, 33.3), 230 (M, 1.7), 213 (18.7), 118 (100.0).

3-phenyl-1-dodecen-1-ol Colourless oil, (anti-isomer) ^1H nmr ($CDCl_3$) δ 0.88 (t, 3H, J= 6.40 Hz), 1.10-1.70 (m, 14H), 3.23 (dd, 1H, J=7.40 and J= 9.08 Hz, PhCH), 3.80 (m, 1H, CH-OH), 5.20 (m, 2H, $=CH_2$), 6.20 (m, 1H, CH=), 7.30 (5H, ArH); ^{13}C nmr ($CDCl_3$) δ 14.84, 23.29, 26.00, 29.79, 30.09 (2C), 32.38, 34.90, 57.63, 73.99, 117.34, 126.02, 127.37, 128.05, 137.62, 140.93; IR (neat) 3305, 1637, 1417, 1037, 892 cm^{-1}; MS (FAB) m/z 260 (M, 4.11%), 259 (17.3), 243 (46.9), 157 (18.7), 154 (56.1), 141 (38.8), 137 (51.9), 131 (56.6), 117 (100.0), 105 (92.5), 91 (98.3).

2-Methyl-1-phenyl-3-buten-1-ol : ^1H nmr ($CDCl_3$) A 50:50 mixture of the anti and syn compounds were obtained. The following signals of the anti and syn product coincide: δ 7.32 (5H,), 5.60-6.00 (m,1H), 4.90-5.30 (m, 2H, $=CH_2$) 2.40-2.70 (m, 1H). Anti : 4.63(d, 1H, J= 8.0 Hz), 1.02 (d, 3H, J=7.0 Hz) Syn 4.38 (d, 1H, J=8.0 Hz), 0.88 (d, 3H, J=7.0 Hz) ^{13}C nmr ($CDCl_3$) δ Aromatic signals for both isomers: 125.00-144.00 Anti 14.10, 44.6, 77.20, 115.3, 134.2 Syn: 16.4 46.1, 77.30, 116.50, 140.10; IR (neat) 3400, 1600, 1455, 1050, 1030, 910 cm^{-1}.[13]

2,2-Dimethyl-1-phenyl-3-buten-1-ol ; ^1H nmr ($CDCl_3$) δ 0.90 (s, 3H), 0.92 (s, 3H) 4.40 (s, 1H, CH-OH), 5.20 (dd, 2H, J= 10.74 and 17.40 Hz, $=CH_2$), 5.95 (dd, 1H, J= 10.74 and 17.40 Hz, CH=), 7.30 (5H, ArH); ^{13}C nmr ($CDCl_3$) δ 21.80, 25.08, 42.54, 80.61, 113.34, 126.79, 126.87, 127.19, 140.07, 144.29; IR (neat) 3305, 1637, 1417, 1037, 892 cm^{-1}.[13]

2,4-Dimethyl-5-hexen-3-ol ; (anti-isomer) ^1H nmr ($CDCl_3$) δ 0.85-1.30 (9H), 1.75 (m, 1H), 2.35 (m, 1H), 3.15 (t, 1H, J= 6.0 Hz) 5.15 (m, 2H, $=CH_2$), 5.80 (m,

1H, CH=); ^{13}C nmr ($CDCl_3$) δ 17.27, 17.67, 20.46, 30.89, 41.63, 79.67, 115.75, 139.46; IR (neat) 3405, 3080, 1637 cm^{-1}.[16]

3,5,5--Trimethyl-1-hexen-4-ol ; (anti-isomer) ^1H nmr ($CDCl_3$) δ 5.96 (m, 1H), 5.05 (m, 2H), 3.14 (d, 1H, J= 5 Hz), 2.52-2.64 (m, 1H), 1.12 (d, 3H, J= 6.5 Hz), 0.94 (s, 9H); ^{13}C nmr ($CDCl_3$) δ 20.69, 26.68, 26.89, 39.35, 82.74, 115.38, 140.20; (syn-isomer) ^1H nmr $CDCl_3$) δ 5.96 (m, 1H), 5.05 (m, 2H), 3.24 (d, 1H, J= 4.5 Hz), 2.52-2.64 (m, 1H), 1.05 (d, 3H, J=6.5 Hz), 0.96 (s, 9H). ^{13}C nmr ($CDCl_3$) δ 14.64, 26.80, 35.83, 39.54, 81.34, 113.15, 144.32; IR (neat) 3480, 3079, 2957, 2874, 1647, 1475, 1364, 909.[17]

1-Isopropyl-2-carbomethoxy-3-buten-1-ol : Colourless oil; (anti-isomer) ^1H nmr ($CDCl_3$) δ 0.94 (d, 3H, J= 6.5 Hz), 1.01 (d, 3H, J= 6.5 Hz), 1.58 (s, 1H, OH), 1.68 (m, 1H, Me_2CH), 3.24 (dd,1H, J= 5.80 and 8.80 Hz, CHCOOMe), 3.62 (dd, 1H, J=4.28 and 5.80 Hz, CH-OH), 3.71 (s, 3H), 5.21 (m, 2H, $=CH_2$), 5.98 (m, 1H, CH=); ^{13}C nmr ($CDCl_3$) δ 17.78, 19.04, 30.74, 52.10, 53.37, 76.23, 120.22, 131.74, 174.05; IR (neat) 3340, 1708, 1640, 1037, 850 cm^{-1}; MS CI (NH_3) m/z 191 (M + NH_4, 7.8), 190 (73.6), 173 (M, 100.0), 155 (45.3),141 (16.1), 123 (17.6).

1-Phenyl-2-carbomethoxy-3-buten-1-ol : yellow oil; (anti-isomer) ^1H nmr ($CDCl_3$) δ 2.90 (br, s, 1H), 3.35 (dd,1H, J= 5.86 and 8.88 Hz, CHCOOMe), 3.61 (s. 3H), 5.02 (d, 1H, J= 5.86, CH-OH), 5.21 (m, 2H, $=CH_2$), 5.98 (m, 1H, CH=); ^{13}C nmr ($CDCl_3$) δ 52.02, 58.18, 73.82, 120.70, 126.31, 127.88, 128.26, 131.62, 140.61, 174.05; IR (neat) 3350, 1715, 1635, 1414, 1030, 883, cm^{-1}; MS CI (NH_3) m/z 224 (M + NH_4, 4.6), 206 (M, 86.6), 189 (100.0),157 (6.8), 121 (9.6).

1-Furfuryl-2-carbomethoxy-3-buten-1-ol: yellow oil; (anti-isomer) ^{1}H nmr ($CDCl_3$) δ 2.90 (d, 1H, J= 4.28 Hz), 3.55 (dd,1H, J= 5.85 and 8.78 Hz, CHCOOMe), 3.68 (s, 3H), 5.05 (dd, 1H, J=4.28 and J= 5.85 Hz, CH-OH), 5.30 (m, 2H, $=CH_2$), 5.95 (m, 1H, CH=), 6.30 (m, 2H), 7.35 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 52.22, 55.05, 68.19, 107.21, 110.19, 120.75, 131.44, 142.19, 153.32, 172.52; (syn-isomer) ^{1}H nmr δ 3.02 (d, 1H, J= 4.3 Hz), 3.65 (dd,1H, J= 5.80 and 8.9 Hz, CHCOOMe), 3.73 (s, 3H), 4.95 (dd, 1H, J=4.30 and 5.80 , CH-OH), 5.18 (m, 2H, $=CH_2$), 5.72 (m, 1H, CH=), 6.30 (m, 2H), 7.35 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 52.26, 54.97, 68.60, 107.76, 110.11, 119.85, 131.37, 142.38, 153.47, 172.95; IR (neat) 3346, 1646, 1031, 849, 631 cm^{-1}; MS CI (NH_3) m/z 214 (M + NH_4, 0.6), 196 (M, 14.8), 179 (100.0), 97 (16.5), 68 (13.1).

E, Z-2,-methyl-6-trimethysilyl-5-hexen-3-ol; (E-isomer) ^{1}H nmr ($CDCl_3$) δ 0.05 (s, 9H), 0.95 (6H), 1.70 (m, 1H), 2.20-2.50 (m, 2H), 3.40 (m, 1H), 5.78 (d, 1H, J= 16.98 Hz), 6.03 (m, 1H); ^{13}C nmr ($CDCl_3$) δ -1.24, 17.54, 18.66, 33.15, 41.84, 75.16, 134.41, 143.33; (Z-isomer) ^{1}H nmr ($CDCl_3$) δ 0.13 (s, 9H), 0.95 (6H), 1.70 (m, 1H), 2.20-2.50 (m, 2H), 3.40 (m, 1H), 5.70 (d, 1H, J= 10.0 Hz), 6.35 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 0.25, 17.50, 18.69, 33.26, 37.88, 75.81, 132.91, 144.96; IR (neat) 3305, 1637, 1417, 1037, 892. [17]

E, Z-2,-methyl-6-phenyldimethysilyl-5-hexen-3-ol; (E-isomer) ^{1}H nmr ($CDCl_3$) δ 0.30 (s, 6H), 0.92 (d, 3H, J= 2.2 Hz), 0.96 (d, 3H, J= 2.2 Hz), 1.68 (m, 1H), 2.10-2.45 (m, 2H), 3.45 (m, 1H), 5.92 (m, 1H), 6.15 (m, 1H); ^{13}C nmr ($CDCl_3$) δ -1.58, 18.20, 19.40, 33.74, 42.39, 75.24, 127.16, 128.31, 129.78, 131.32, 133.08, 144.56; (Z-isomer) ^{1}H nmr ($CDCl_3$) δ 0.40 (s, 6H), 0.82 (6H), 1.70 (m, 1H), 2.10-2.50 (m, 2H), 3.35 (m, 1H), 5.82 (m, 1H), 6.47 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 0.01,

17.99, 19.22, 33.74, 38.42, 75.90, 127.26, 128.31, 129.78, 131.32, 133.08, 146.02; IR (neat) 3320, 1620, 1418, 984.

E-2,7,7-trimethyl-5-octen-3-ol ; (E-isomer) ^{1}H nmr ($CDCl_3$) δ 0.95 (6H), 1.65 (m, 1H), 1.95-2.30 (m, 2H), 3.30 (m, 1H), 5.35 (m, 1H), 5.60 (d, 1H, J= 15.54 Hz); ^{13}C nmr ($CDCl_3$) δ 18.33, 19.42, 30.26, 31.74, 33.52, 38.17, 75.52, 120.28, 144.93.[18]

*The coupling of (-)-myrtenyl bromide (**2.10**) to isobutyraldehyde:* To a solution of the isobutyraldehydes(0.072g, 1 mmol) and myrtenyl bromide (0.430g, 2 mmol) in 2ml of H_2O, was slowly added indium powder(150 mesh, 0.230g, 2 mmol). The reaction mixture was vigorously stirred at room temperature for 3-4 hrs. The product mixture was extracted with ether and the separated organic layer washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography (hexane: ethyl acetate 20:1). Isolated yield 187 mg (90 %) ; ^{1}H nmr ($CDCl_3$) 0.73 (s, 3H), 0.90 (d, 3H, J= 6.0 Hz),1.05 (d, 3H, J= 6.0 Hz),1.25 (s, 3H), 1.35 (m, 1H), 1.58 (m, 1H), 1.95-2.05 (m, 3H), 2.40 (m, 1H), 2.45-2.60 (m, 2H), 3.20 (dd, 1H, J= 1.0 and 4.0 Hz), 4.70 (s, 1H), 4.90 (s, 1H); ^{13}C nmr ($CDCl_3$) δ 15.25, 21.93, 22.21, 26.31, 26.78, 28.69, 30.31, 39.49, 41.08, 41.66, 52.54, 79.00, 110.72, 151.88; MS (FAB) m/z 208 (M, 1.9), 154 (100.0), 138 (36.9), 136 (88.8), 107 (35.9), 91 (37.5).

General procedure for addition of allyl halides to aromatic and aliphatic carbonyl compounds using bismuth metal: To a mixture of the aldehydes or ketone (1 mmol), allyl iodide (2 mmol), tetra-n-butylammonium bromide (1 mmol) in 15ml of H_2O , was added bismuth powder (2mmol, 100 mesh). The

reaction mixture was vigorously stirred at room temperature for 5-24 hrs. The product mixture was extracted with ether and the separated organic layer washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography (hexane: ethyl acetate).

1-Phenyl-3-buten-1-ol : ^1H nmr ($CDCl_3$) δ 2.28 (d, 1H, J= 3.05 Hz), 2.45 (m, 2H), 4.65 (td, 1H, J=3.05 and 7.16 Hz), 5.08 (m, 2H, $=CH_2$), 5.74 (m, 1H, CH=), 7.30 (5H, ArH); ^{13}C nmr ($CDCl_3$) δ 44.21, 73.30, 117.91, 125.19, 126.92, 127.77, 133.74, 143.02; IR (neat) 3400, 1640, 1500, 1450, 1040, 910, 750 cm^{-1}; MS CI (NH_3) m/z 166 (M + NH_4, 2.4), 148 (M, 28.8), 131 (100.0), 107 (41.6), 79 (43.9), 77 (30.8).[10b]

1-(4-Chlorophenyl)-3-buten-1-ol : ^1H nmr ($CDCl_3$) δ 2.15 (s, 1H), 2.45 (m, 2H), 4.68 (td, 1H, J=2.58 and 7.42 Hz), 5.08 (m, 2H, $=CH_2$), 5.74 (m, 1H, CH=), 7.30 (4H, ArH); ^{13}C nmr ($CDCl_3$) δ 44.24, 72.58, 118.35, 126.59, 127.89, 132.45, 133.27, 141.48; MS CI (NH_3) m/z 202 (M + 2 + NH_4, 0.6) 200 (M + NH_4, 1.7), 184 (M + 2, 9.3), 182 (M, 28.6), 167 (32.8), 165 (100.0) 141 (51.6);[14]

1-(4-Nitrophenyl)-3-buten-1-ol : ^1H nmr ($CDCl_3$) δ 2.10 (s, 1H), 2.59 (m, 2H), 4.85 (m, 1H), 5.08 (m, 2H, $=CH_2$), 5.80 (m, 1H, CH=), 7.40-8.40 (4H, ArH); ^{13}C nmr ($CDCl_3$) δ 44.26, 72.16, 119.13, 123.04, 123.08, 125.93, 132.49, 150.17; IR (neat) 3450, 1640, 1450, 1345 cm^{-1}; MS CI (NH_3) m/z 211 (M + NH_4, 100.0), 193 (M, 6.5), 153 (21.9), 135 (15.2).

1-(4-Biphenyl)-3-buten-1-ol : ^1H nmr ($CDCl_3$) δ 2.10 (s, 1H), 2.50 (m,2H), 4.80 (dd, 1H, J= 5.78 and 7.24 Hz), 5.08 (m, 2H, $=CH_2$), 5.80 (m, 1H, CH=), 7.30 (5H,

ArH); ^{13}C nmr ($CDCl_3$) δ 44.19, 75.05, 118.06, 125.65, 126.45, 126.55, 126.64, 128.18, 133.69, 139.68, 140.03, 142.06; IR (neat) 3400, 1640, 1050, 930 cm^{-1}; MS CI (NH_3) m/z 242 (M + NH_4, 0.4), 224 (M, 2.7), 207 (100.0), 183 (63.2) 155 (24.7).

1-Dodecen-4-ol : ^1H nmr ($CDCl_3$) δ 0.90 (t, 3H, J= 6.40 Hz), 1.20-1.55 (br, 14H), 1.65 (s, 1H), 2.00-2.40 (m, 2H), 3.65 (br m, 1H), 5.15 (m, 2H, $=CH_2$), 5.85 (m, 1H, CH=); ^{13}C nmr ($CDCl_3$) δ 14.08, 22.65, 25.65, 29.25, 29.55, 29.64, 31.86, 41.92, 70.67, 118.02, 134.92; IR (neat) 3550, 3000, 1650, 1470, 910 cm^{-1}; MS CI (NH_3) m/z 202 (M + NH_4, 100.0), 184 (M, 4.7), 143 (62.5), 125 (30.7), 111 (11.1).

4- tert-Butyl-1-(2-propenyl)cyclohexanol : ^1H nmr ($CDCl_3$) δ 0.87 (s, 9H), 1.00-1.85 (m, 8H) 2.50 (d, 2H, J= 7.24 Hz), 5.15 (m, 2H, $=CH_2$), 5.85 (m, 1H, CH=); ^{13}C nmr ($CDCl_3$) δ 24.90, 28.22, 38.93, 41.35, 47.78, 77.63, 118.37, 132.99; IR (neat) 3375, 3000, 1640, 1050, 910 cm^{-1};[15]

1- Allylcyclohexanol : ^1H nmr ($CDCl_3$) δ 1.40-1.70 (m, 10H) 2.25 (d, 2H, J= 7.45 Hz), 5.08-5.24 (m, 2H, $=CH_2$), 5.83-6.00 (m, 1H, CH=); IR (neat) 3375, 3000, 1640, 1050, 910 cm^{-1}.[15]

Synthesis of Methyl 2-(α-Hydroxy-4-nitrobenzyl-) but-3-enoate: To a mixture of the p-nitrobenzaldehyde (0.151 g, 1 mmol), methyl 4-bromocrotonate (0.358 g, 2 mmol) tetra-n-butylammonium bromide (0.322 g, 1 mmol) in 15ml of H_2O , was added bismuth powder(0.416 g, 2mmol, 100 mesh). The reaction mixture was vigorously stirred at room temperature for 12 hrs. The product mixture was extracted with ether and the separated organic layer washed with brine, dried

with $MgSO_4$ and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography (hexane: ethyl acetate) giving the product in 80% yield (154 mg).light yellow crystals (recrystallized from isopropyl ether, IPE); m.p. 71-73°C; (anti-isomer) ^1H nmr ($CDCl_3$) δ 3.31 (dd,1H, J= 5.00 and 9.00 Hz, CHCOOMe), 3.33 (d, 1H, J= 2.50 Hz, -OH), 3.67 (s, 3H), 5.08 (dd, 1H, J= 1.00 and 17.00 Hz), 5.20 (dd, 1H, J= 2.50 and 5.00 Hz, -CHOH), 5.25 (d, 1H, J= 10.00 Hz) 5.98 (ddd, 1H, J= 9.00, 10.00 and 17.00 Hz CH=), 7.40-8.40 (4H, ArH); ^{13}C nmr ($CDCl_3$) δ 52.39, 57.40, 72.76, 121.75, 123.45, 127.17, 130.11, 147.82, 172.91; IR (neat) 3440, 1710, 1630, 1430, 1340 cm^{-1}; MS CI (NH_3) m/z 269 (M + NH_4, 95.4), 251 (M, 23.2), 234 (100.0),151 (68.9), 135 (24.2), 122 (45.0).

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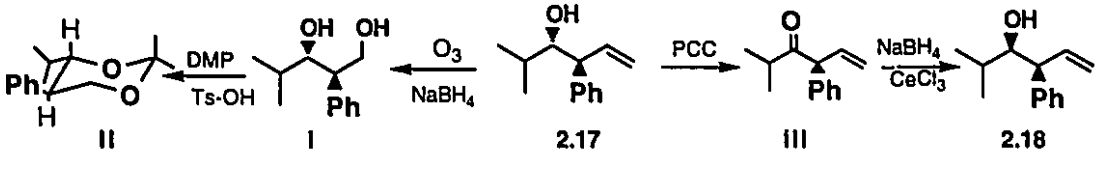
9. 

II I 2.17 III 2.18

The anti stereochemistry of the major isomers was deduced by converting the purified diastereomer **2.17** (entry 4, Table 2.1) to diol **I** followed by acetal formation of **II** The anti relationship of the phenyl and

isopropyl group was evident from the vicinal coupling constant (J=11.2 Hz) of the ring methine protons in **II**. The presence of the minor isomer **2.18** in the original isomeric mixture was confirmed by comparison of the 1H nmr of the mixture with that of an authentic sample prepared independently from **2.17**. **2.17** was first oxidised to ketone **III** which was then reduced by $NaBH_4$/ $CeCl_3$ to give **2.18**.

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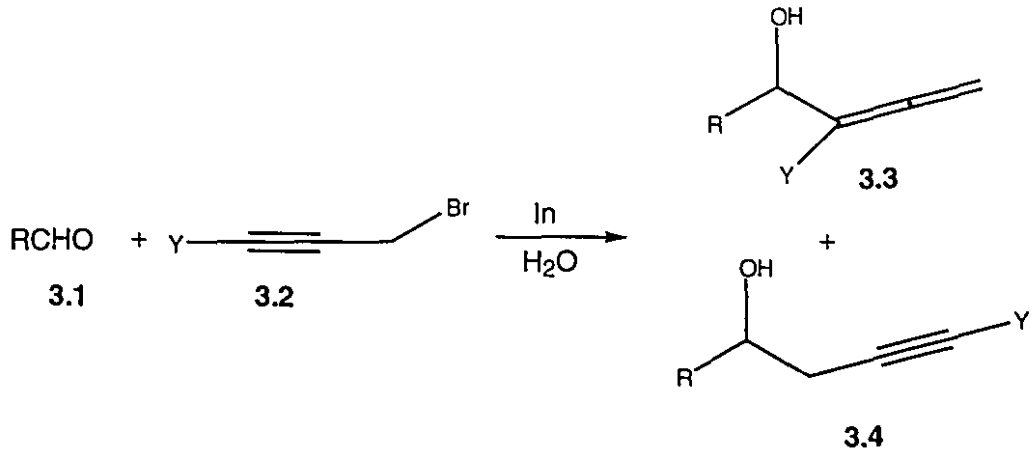
Chapter 3

Indium-Mediated Coupling of Aldehydes with Prop-2-ynyl Bromides in Aqueous Media. Regioselective Synthesis α-Allenic Alcohols

3.1 Introduction

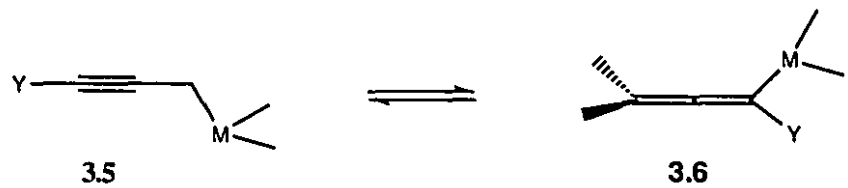
Metal-mediated reactions in aqueous media have recently stimulated considerable interest in their application to organic synthesis. Particularly well known is the coupling of allylic halides with carbonyl compounds in aqueous media to give the corresponding homoallylic alcohols[1,2]. Such organometallic-type reactions in aqueous media have already been shown to offer a number of advantages over conventional organometallic reactions in organic solvents in that: (1) the need for inflammable anhydrous organic solvent is obviated; (2) protection of 'reactive' hydroxy or acidic functional groups is no longer required; (3) compounds insoluble in organic solvents (e.g. carbohydrates) can react directly; and (4) possible change in selectivity owing to the change from organic solvent to aqueous media. Variations in the allylic theme for the allylation of carbonyl compounds in aqueous media have been the use of 1,3-dihalopropenes,[3] 2-chloromethyl-3-iodopropene,[4] 2-bromomethylacrylates[5] and 2-bromomethylacrylic acid.[6] More recently, 2-chloromethyl-3-chloropropene has been used by Li et. al in a tandem alkylation-aqueous indium-mediated cyclization of 1,3-dicarbonyl compounds in the construction of cyclopentanoids.[7] It would seem reasonable therefore to extend the coupling reaction to prop-2-ynyl halides **3.2** according to scheme 3.1. Indeed, the coupling between prop-2-ynyl bromide (**3.2a**, Y=H) with aldehydes mediated by tin in aqueous media has been examined.[8] The reaction was found to give a

mixture of regioisomers (**3.3** and **3.4**) in nearly equal proportions and thus was synthetically not too useful.



Scheme 3.1

α-Allenic (**3.3**) and homopropargylic (**3.4**) alcohols are valuable intermediates in organic synthesis as these structural units are present in a variety of natural products and biologically active compounds.[9] Synthesis of these compounds are generally accomplished by reactions involving propargylic (**3.5**) or allenic (**3.6**) anion equivalents. The utility of organometallic derivatives of types **3.5** or **3.6** in such a methodology is unfortunately limited due to their ambident nucleophilic nature allowing them to react with electrophiles unselectively to produce a mixture of allenic (**3.3**) and acetylenic (**3.4**) products. Furthermore, the presence of other functional groups, such as esters or nitriles, in the substrate is not tolerated by these organometallics, restricting the use of these reagents in the total synthesis of complex natural products.



3.5 **3.6**

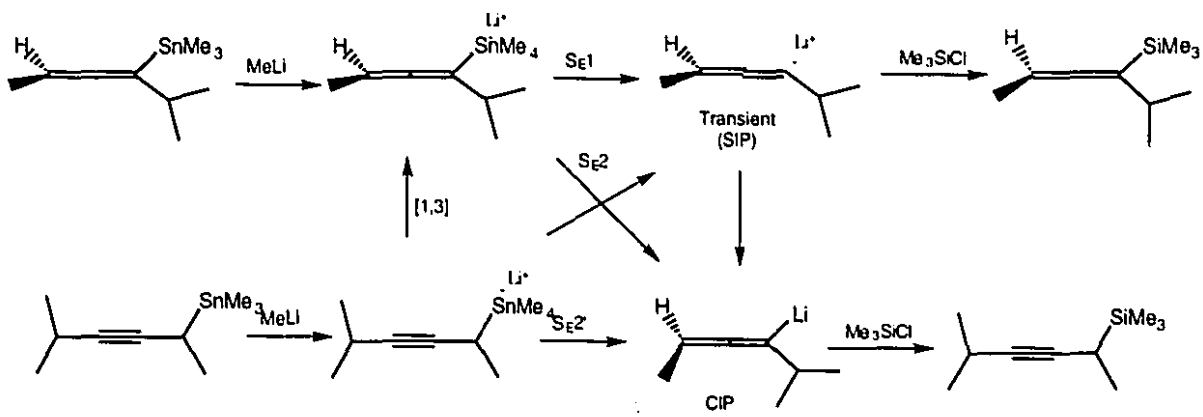
Allenic and propargylic organometallic reagents using an array of metals such as magnesium, lithium, titanium, zinc, aluminum, tin, silicon and boron, have been tested in recent years for regiospecific synthesis of allenic and homopropargylic alcohols, and it has been established that they react with aldehydes with variable regioselectivity affording mixtures of **3.3** and **3.4**. Furthermore, the regioselectivity seems to be dependent on the kind of metal used. For example, zinc,[14] boron,[29] and tin,[8] magnesium,[30] lithium[31] reagents show propargylic selectivity whereas aluminium[14] reagents exhibit allenic selectivity. This regiochemical ambiguity arises from the fact that these species generally exist as an equilibrium mixture of allenic and propargylic organometallic derivatives.

3.2 Preparation of propargylic and allenic organometallics

Organometallics of allenic structure are usually prepared by the reaction of metals with propargylic halides or allenic halides, or by metallation with alkyl lithium of the corresponding hydrocarbons. Prevost, in 1950, prepared the first allenylmagnesium bromide.[10] Allenylzinc bromides were later easily obtained in high yields by the direct reaction of the propargyl bromide at -100°C with zinc in anhydrous THF.[11] Nmr studies on the Grignard reagent obtained from various propargylic bromides show in all cases that a rapid equilibrium exist between the allenic and alkynic forms.[12]

Recently, Riech et. al reported a detailed NMR study of the allenyl/ propargyl lithium species investigating the factors affecting the allenic-propargylic equilibrium.[13] A pair of allenyl (5-methyl-4-(trimethylstannyl)-2,3-hexadiene) and propargyl (5-methyl-2-(trimethylstannyl)-3-hexyne) stannanes

were prepared and used in a series of lithium-tin exchange experiments. Both allenyl and propargyl stannanes gave the allenyl lithium species on treatment with CH_3Li in THF at -78°C as shown by NMR spectroscopy. Subsequent trapping of the allenyl lithium with TMS-Cl (the sequential experiment) gave the propargylsilane as the major product. If the TMS-Cl was present during the lithium-tin exchange (in situ experiment), highly variable ratios of allenyl and propargylsilanes were obtained. The ratio of allenic and propargylic products were different when the trimethylstannyl compounds were treated with CH_3Li in different THF-HMPA solvent mixtures (in situ experiments). However, for a given solvent system identical product ratios were obtained when phenyllithium was used instead of methyllithium, or when the trimethylstannyl reagents were replaced by triphenylstannyl reagents. The kinetic behaviour, solvent effects and the results of the trapping experiments were consistent with a mechanism shown in scheme 3.2



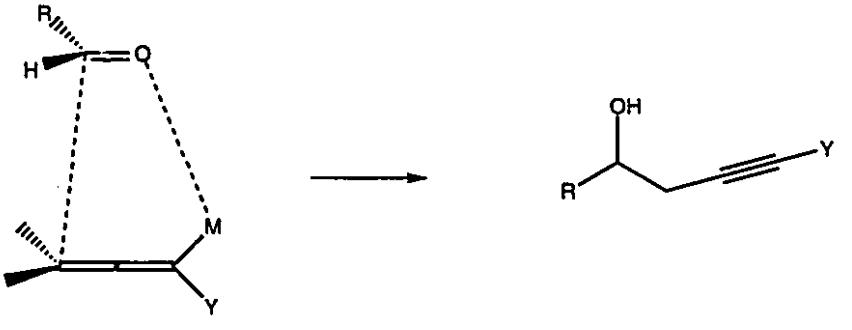
Scheme 3.2

The intermediate tin ate complex (propargylic or allenic) first fragments to a transient solvent-separated ion pair (SIP), which can be trapped to give mainly the allenylsilane. The SIP rapidly collapses to the stable contact ion pair (CIP) which gives mainly the propargylsilane on reaction with silylchlorides. The

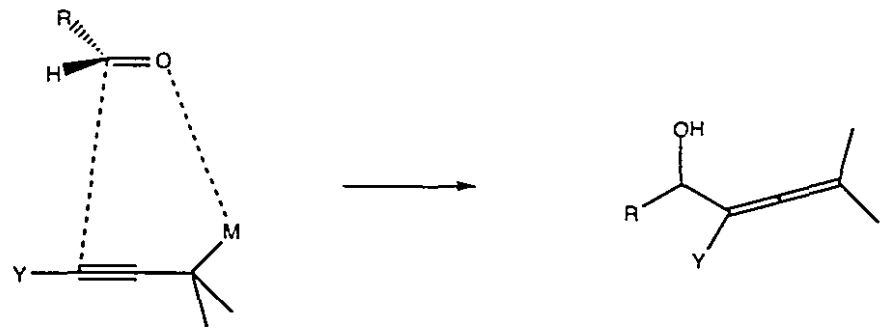
experimental evidence supports the assignment of a separated ion pair structure to the allenic/propargylic intermediate. Similar phenomena should be considered whenever reactive organometallic reagents are generated in situ, or when intramolecular trapping of such intermediates is performed.

3.3 Regioselective reactions of propargylic and allenic organometallics with electrophiles.

The reaction of allenic derivatives with most electrophiles gave mainly or exclusively the alkynic products. This behavior is rationalized by attack at the 3-position, which may be interpreted as an S_E2' reaction of allenyl Grignard compounds. For example, organometallic derivatives combine with carbonyl compounds by the S_E2' pathway to afford the homopropargylic and allenic alcohols from the corresponding allenyl or propargyl organometallics, respectively (Scheme 3.3). The product distribution of these reactions is determined by the position of the equilibrium between the two organometallic intermediates and their relative rates of addition to carbonyl compounds.

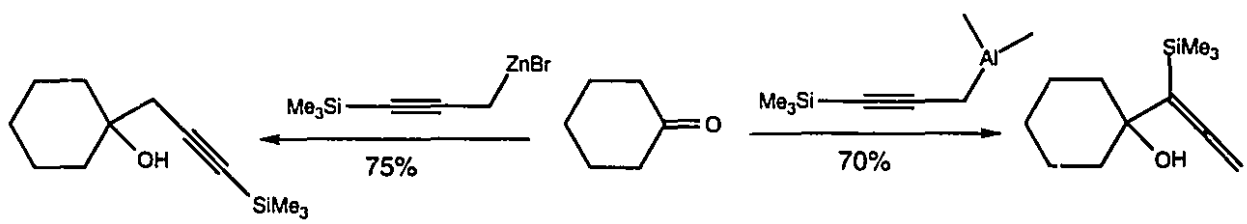


Scheme 3.3



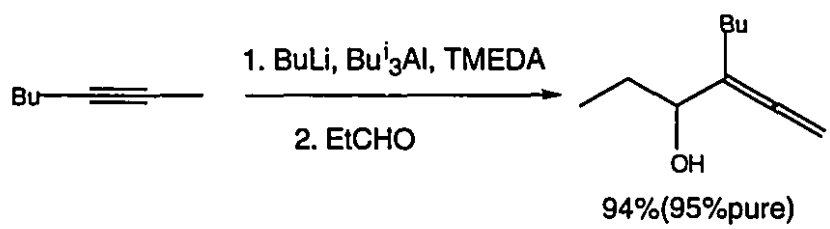
Scheme 3.3 (cont'd)

The organometallic reagent produced by the reaction of trimethylsilylpropargyl bromide with aluminum amalgam in anhydrous THF, condenses readily with aldehydes and ketones to give the allenic alcohols resulting from coupling α to the trimethylsilyl substituent. However the corresponding trimethylsilylpropargylzinc reagent gives the homopropargylic alcohols as the product. (Scheme 3.4).[14]



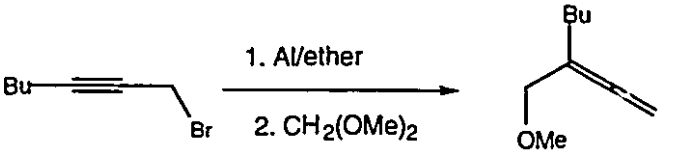
Scheme 3.4

Propargylic lithium alanates or lithium borates react with carbonyl compounds in a regioselective manner to furnish 1, 1-disubstituted allenes (Scheme 3.5).[15]



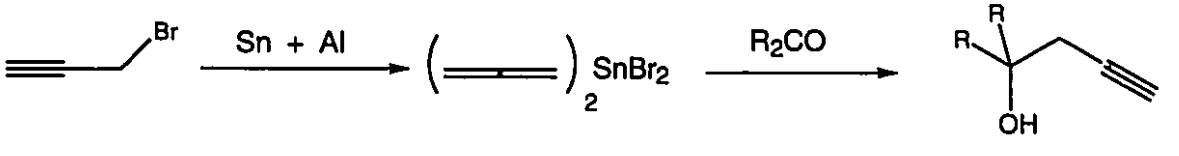
Scheme 3.5

The reaction between alkyl halides and aluminum metal is the basis of the oldest method for the synthesis of organoaluminum compounds. For example, propargylic bromides react with aluminum in ether giving organoaluminum compounds that on treatment with acetals yield solely the α-allenic ether (Eq. 1).[16]

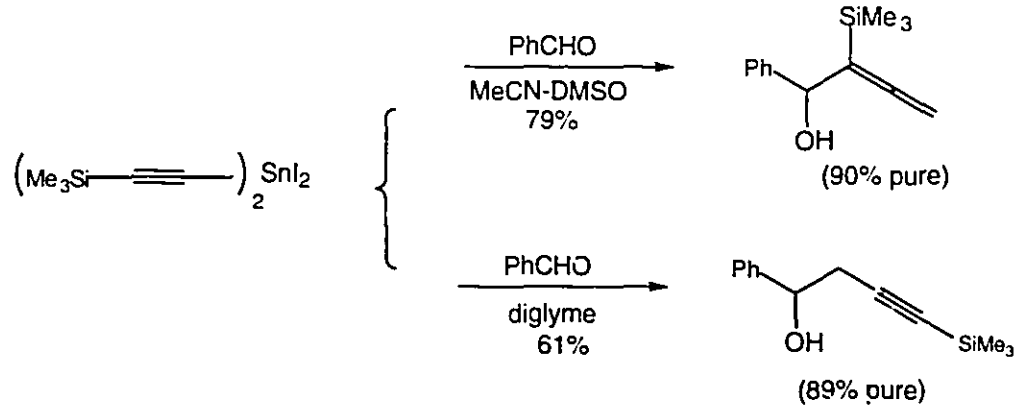


70% (1)

Diallenyltin dibromide, prepared by treatment of propargyl bromide with metallic tin in the presence of metallic aluminum in dry THF, reacts with aldehydes and ketones to afford the homopropargylic alcohols selectively (Scheme 3.6).[17] This result is different from a previous report by Mukaiyama and Harada, who found the α-allenic alcohol to be the major product from a propargyltin reagent derived from a tin (II) halide.[18] On the other hand, homopropargylic and α-allenic alcohols were synthesized selectively by the reaction of aldehydes and ketones with bis(trimethylsilylpropargyl)tin diiodide using different solvent systems (Scheme 3.7).[18]

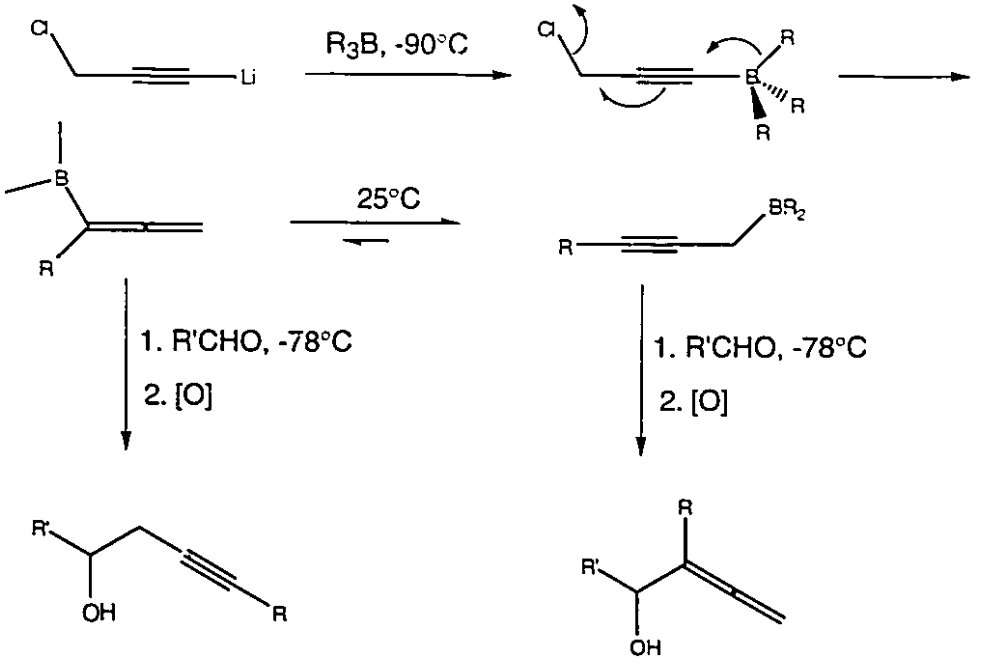


Scheme 3.6



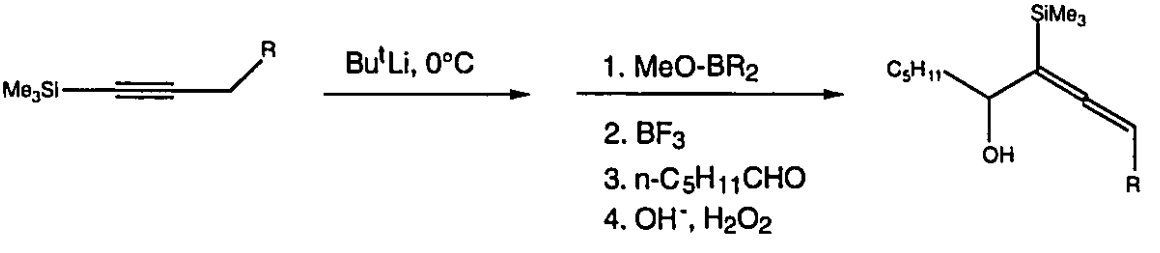
Scheme 3.7

The ate complex of organoborane reagent, formed by the reaction of a trialkylborane with lithium propargylide at -90°C, undergoes a spontaneous anionotropic rearrangement in which one alkyl group migrates from boron to the adjacent carbon concomitant with an electron pair shift and loss of chloride to produce the allenic borane. Treatment of the allenic borane with an aldehyde results in an allenic-propargylic rearrangement to give, after oxidative work-up, a homopropargylic alcohol. However, if the allenic borane initially formed is allowed to warm, it rearranges to the thermodynamically more stable propargylic borane. This in turn reacts with the carbonyl of the aldehyde, with boron transposition, to produce the α-allenic alcohol (Scheme 3.8).[19]



Scheme 3.8

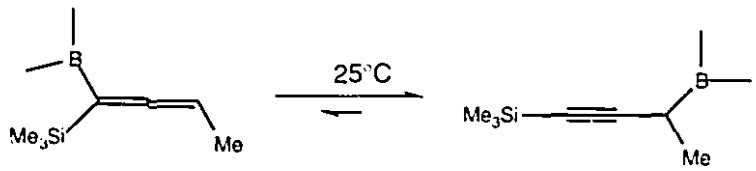
Propargylic organoboranes derived from the corresponding lithium reagents react with aldehydes and certain ketones with high regioselectivity to give trimethylsilyl-sustituted α-allenic alcohols (Scheme 3.9).[20]



Scheme 3.9

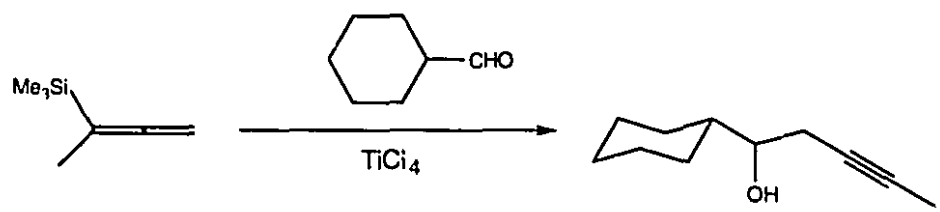
The high regioselectivity in the formation of α-allenic alcohols from boron reagents at low temperature is markedly different from that seen with the titanium reagent derived from 1-trimethylsilyl-1-butyne, in which the exclusive formation of homopropargylic alcohol is observed.[21] This result was explained

by a rapid exchange between the allenic and propargylic structures shown in equation 2. The alkynic structure is thermodynamically less stable and kinetically more reactive than that of the allenic form. At lower temperature, the rate of equilibrium becomes faster than the subsequent reaction with aldehydes and thus the propargylic species becomes the major reaction form.



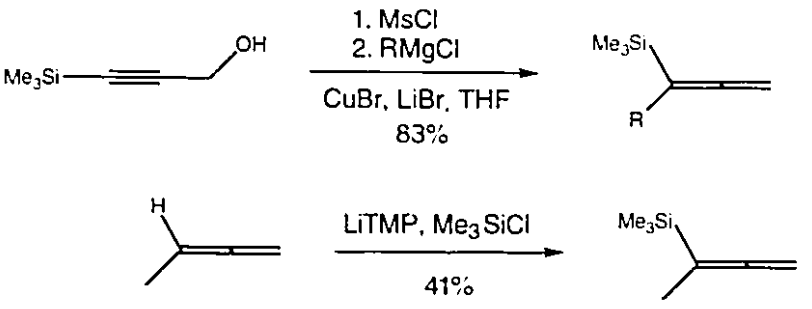
(2)

The reaction of trimethylsilylallenes with aldehydes and ketones in the presence of titanium tetrachloride provides a regiocontrolled route to homopropargylic alcohols of a variety of substitution types. Thus, the addition of 1-alkyl-substituted trimethylsilylallenes to carbonyl compounds furnishes the desired alkynes directly (Scheme 3.10).



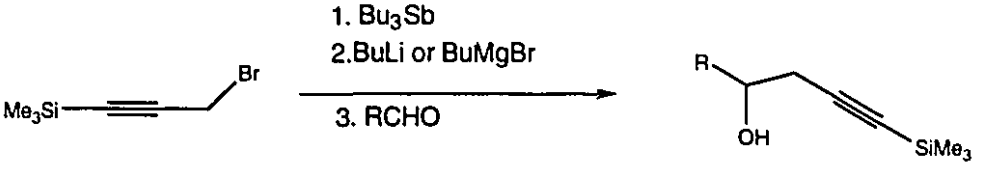
Scheme 3.10

The required allenyl silanes are prepared selectively by the method of copper-catalysed addition or by direct silylation of the lithium derivative of 1,2-butadiene (Scheme 3.11).[22]



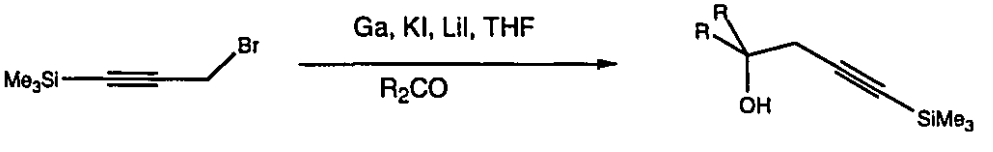
Scheme 3.11

The reaction of trimethylsilylpropargylic organoantimony compounds with aldehydes was found to exhibit very high acetylenic selectivity in the presence of lithium bromide (Scheme 3.12).[23]



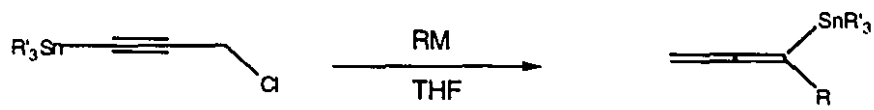
Scheme 3.12

Similarly, one pot reactions of gallium powder, trimethylsilylpropargyl bromide, aldehyde or ketone in the presence of KI and LiI were recently found to give acetylenic compounds selectively (Scheme 3.13).[24]



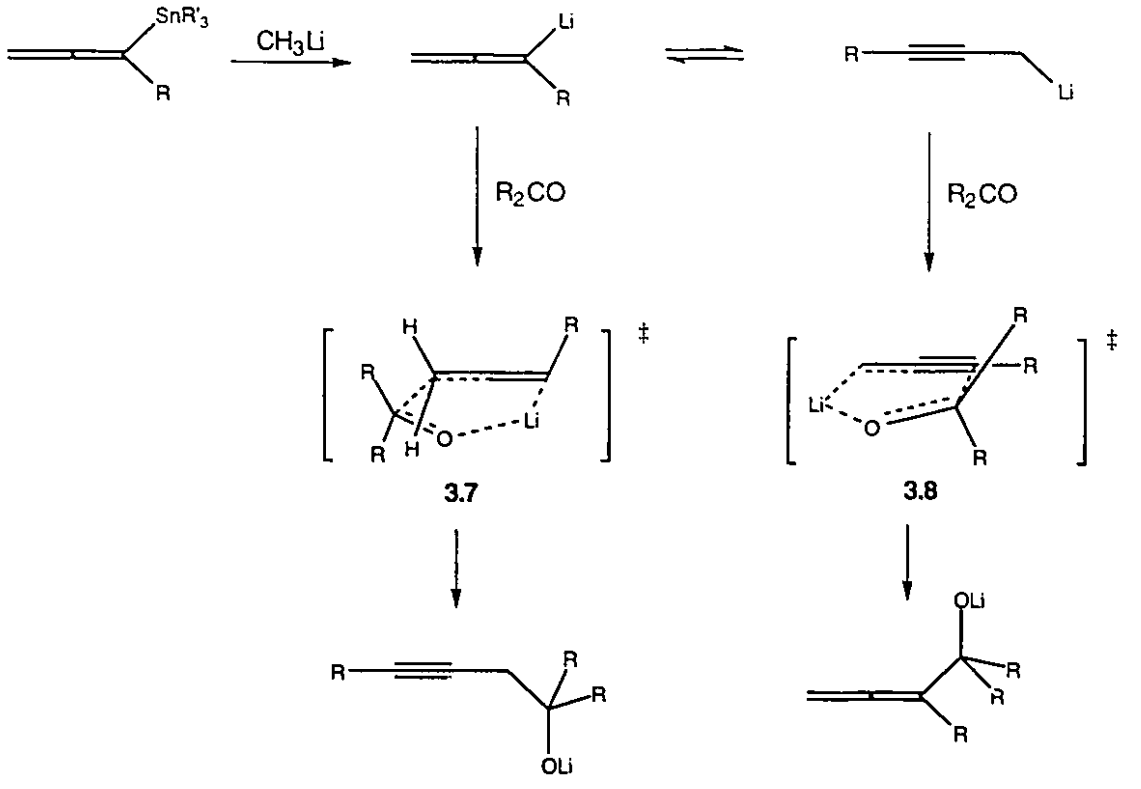
Scheme 3.13

Noyori et al.[25] have recently shown that 1-substituted allenyl trialkylstannanes, prepared as shown in scheme 3.14, readily undergo transmetalation with an alkyllithium to generate the tetraalkylstannanes and an equilibrating mixture of the allenyl and propargyllithium compounds. The organolithium derivatives reacted with aldehydes and ketones at low temperature to give, after aqueous workup, the regioisomeric homopropargylic and α-allenic alcohols in high yields. The degree of regioselection was shown to be highly sensitive to the steric and electronic properties of the carbonyl substrates. Excellent propargylic selectivities were obtainable by a combination of bulky reagents and substrates or by using acylsilanes as the carbonyl components. The origin of the regioselectivity (selective propargylation) is illustrated in scheme 3.15.



RM = i-C_3H_7MgCl or t-C_4H_9MgCl with 3% CuCN

Scheme 3.14



Scheme 3.15

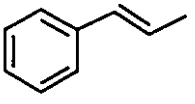
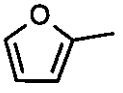
The regioselectivity of the addition of the equilibrating ambident organolithium compounds is determined kinetically by the relative stabilities of transition states **3.7** and **3.8**, which are affected by steric factors. Since the reaction was found to be highly exothermic, these transition structures reflect the nature of the of the starting organolithium and carbonyl compounds (Hammond's postulate). Sterically, **3.7** suffers from H/R eclipsed nonbonding repulsion whereas **3.8** is destabilised by a gauche type R/R interaction. These steric effects become important with bulky R groups thus favoring the homopropargylic product.

3.4 Indium mediated reactions of prop-2-ynl bromides with aldehydes in water as solvent.

With the growing number of regioselective methods for the synthesis of homopropargylic and α-allenic alcohols, there has been a surge of interest in the development of novel routes for α-allenic alcohols. This has arisen as a consequence of the α-hydroxyallene structural feature being contained in many natural substances[9f] and physiologically active compounds.[9g] A number of the latter have proven to be powerful hypertensive and anti-inflammatory agents. The increasing use of indium metal in an aqueous medium prompted us to examine the reaction of prop-2-ynl bromides with aldehydes in water as solvent. The coupling of propargyl bromide with aldehydes mediated by indium in aqueous media was examined briefly without any definite conclusion regarding the regioselectivity issue.[26] We found that using indium as a metal, the coupling reaction was found to be regioselective, and conditions have been discovered that favor either the homopropargylic or the α-allenic alcohols. The results are summarized in Table 3.1.

With the parent prop-2-ynyl bromide (**3.2a**, Y= H Scheme 3.1), indium-mediated coupling with aliphatic or aryl aldehydes (entries 1 and 2) in water gave mainly the homopropargylic alcohols **3.3** in good yields. In contrast, when the prop-2-ynyl bromide is γ-substituted (**3.2b**, Y = Me or **3.2c**, Y = Ph), the coupling products were predominantly or exclusively the α-allenic alcohols.**3.4**, again in good yields. Worthy of note is the reaction of formaldehyde with **3.2c** (entry 4). In this case, the formaldehyde was added as an aqueous solution and must exist mainly in the hydrated form. For the α,β-unsaturated aldehydes (entry 5 and 6), the coupling occurred exclusively in a 1,2-fashion.

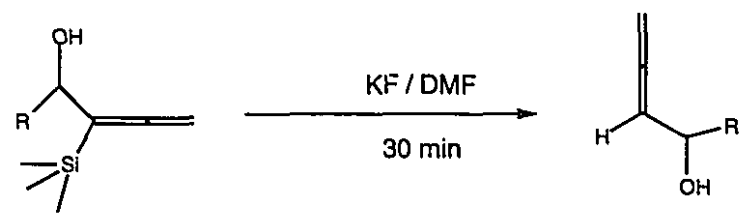
Table. 3.1 Indium mediated coupling of prop-2-ynyl systems with aldehydes in water

Entry	Aldehyde (**3.1**) R =	Prop-2-ynyl bromides	Combine yields (%)	Allene : Acetylene
1	$n\text{-}C_8H_{17}$	$BrCH_2CCH$	97	12 : 88
2	1-Napthyl	$BrCH_2CCH$	50	10 : 90
3	$n\text{-}C_8H_{17}$	$BrCH_2CCPh$	89	95 : 5
4	H	$BrCH_2CCPh$	94	99 : 1
5	BuCC	$BrCH_2CCPh$	93	90 : 10
6		$BrCH_2CCPh$	96	99 : 1
7		$BrCH_2CCPh$	75	93 : 7
8	$n\text{-}C_8H_{17}$	$BrCH_2CCMe$	99	100 : 0
9	1-Napthyl	$BrCH_2CCMe$	98	100 : 0
10	Ph	$BrCH_2CCSiMe_3$	60	80 : 20
11	$n\text{-}C_8H_{17}$	$BrCH_2CCSiMe_3$	82	67 : 33
12	1-Napthyl	$BrCH_2CCSiMe_2Ph$	70	80 : 20
13	Me_2CH	$BrCH_2CCSiMe_2Ph$	60	80 : 20

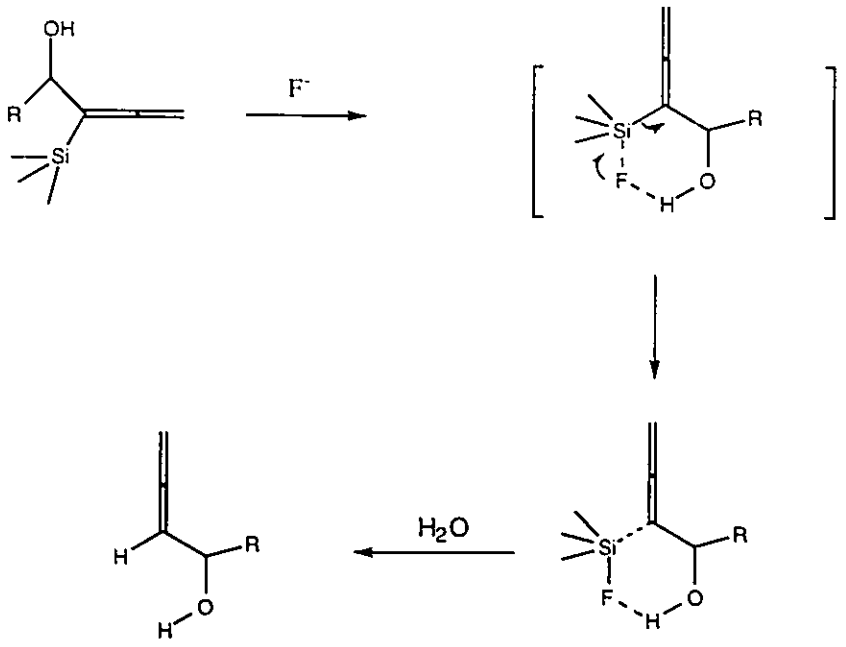
Based on the above observation, an approach was devised to obtain selectively the unsubstituted α-allenic alcohol **3.3** (Y = H). 1-Silyl-3-bromopropyne (**3.2d**, Y= Me_3Si or **3.2e**, Y = Me_2PhSi) was coupled with aldehydes (entries 10-13), to give the corresponding α-allenic alcohols **3.3** (Y= Me_3Si or Me_2PhSi), which could be readily separated from the minor isomeric

prop-2-ynyl product **3.4** by flash chromatography. Protodesilylation of **3.3** (Y= Me_3Si or Me_2PhSi) with KF/DMF gave quantitatively the unsubstituted allenic alcohols **3.3** (Y = H) without contamination with isomer **3.4** (Y = H) (Scheme 3.16).The protodesilylation reaction by fluoride ion is patterned after a similar reaction on β-hydroxyvinylsilanes developed in this lab.[27] Even though the reaction has since been applied to numerous systems, this is the first example of a protodesilylation reaction on an allenylsilane (Scheme 3.17). In view of the increasing use of allenyl alcohols as building blocks in organic synthesis, the present indium-mediated coupling reaction may find useful application.[28]

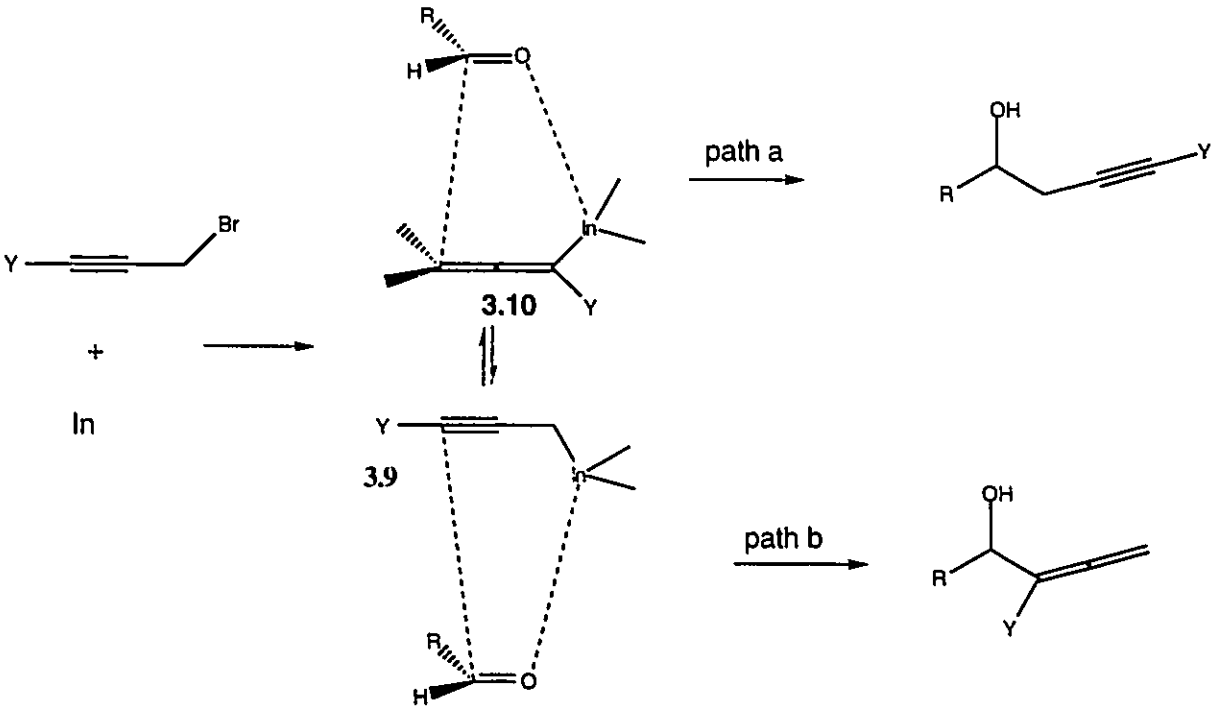
To account for the above regioselective outcome, the following mechanism can be proposed in broad terms for the indium-mediated coupling of prop-2-ynyl bromides with aldehydes in aqueous media. First, a propargyl indium species **3.9** is formed which exists in equilibrium with its regioisomer **3.10** (Scheme 3.18).



Scheme 3.16



Scheme 3.17



Scheme 3.18

In the case of propargyl bromide (Y = H), the allenic indium species is presumably the thermodynamically more stable species under the reaction conditions. In the coupling with aldehydes, the reaction proceeds predominantly through 'path a' giving rise to the homopropargylic alcohol as the major product. However, in the cases where there is a γ-substituent in the prop-2-ynyl bromide, the corresponding allenic indium species is destabilized (probably through steric interactions of Y with In and its surrounding ligands) thereby favoring the formation of the α-allenic alcohols via 'path b'.

The regiochemical selectivity of propargylic/allenic systems has also been found to be dependant upon the solvation environment.[14] Provided that the equilibrium between **3.9** and **3.10** is not rate determining, then the product distribution can also be explained by the relative kinetic stability of the two reactive organoindium transition states in water as solvent. In other word, the different hydrophobic interactions of the two possible transition states exposed to the aqueous environment probably renders 'path b' kinetically more favorable than 'path a'. In this connection, however, the contributing electronic influence of substituents such as Y= Me_3Si or Me_2PhSi on regioselectivity should not be ignored.

In summary, a new method has been developed for the regioselective allenylation of carbonyl compounds in aqueous media mediated by indium metal. The method illustrates a convenient and highly regioselective protocol toward the synthesis of both homopropargylic and α-allenic alcohols.

Experimental

General. Chemicals were purchased from Aldrich and were reagent grade. Except for propargyl bromide (**3.2a**, Y = H), which was commercially available, all other prop-2-ynyl bromides were prepared from the corresponding commercial prop-2-ynyl alcohol using PBr_3 in ether. Analytical thin layer chromatography was performed on silica gel 60 F_{254} plastic back 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 (10 ml / 90 ml) and heated with a heat gun.

The Nuclear Magnetic Resonance spectra were recorded on a VARIAN Gemini 200 (^1H 500 MHz, ^{13}C 50 MHz) or a Unity 500 MHz (^1H 200 MHz, ^{13}C 125 MHz) spectrometer and chemical shifts are reported on the δ scales in parts per million (ppm) with solvent residue as references. Singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) were recorded at the centre of the peaks and were used throughout. IR spectra were recorded on an Analet FT A25-18 spectrometer between NaCl plates. Mass spectra were recorded on a Kratos MS25RFA mass spectrometer.

General procedure for the coupling of prop-2-ynyl bromides with aldehydes : To a mixture of the aldehyde (1 mmol) and prop-2-ynyl bromide (2 mmol) in H_2O (2ml), was slowly added indium powder (150 mesh, 2 mmol). The reaction mixture was vigorously stirred at room temperature for 5-7 hrs. The mixture was then extracted with diethylether (2 x 10 ml), filtered, and the filtrate washed (water). The organic layer was separated, washed (brine) and dried ($MgSO_4$). The solvent was evaporated and then purified by flash chromatography (hexane: ethylacetate).

General procedure for the Protodesilylation of the Silyl substituted α-allenic alcohols: To a solution of the silane (0.2 mmol) in DMF (1.5-2.0 mls) was added KF (0.25 mmol) The reaction mixture was stirred for a period of time until the reaction was judged complete by TLC. The mixture was poured into water (2 mls), extracted with diethyl ether. The ether layer was separated, washed with brine and dried (MgSO4). The solvent was then evaporated and the crude product purified by flash chromatography (hexane: ethylacetate).

1-Dodecyn-4-ol : ^{1}H NMR ($CDCl_3$) δ 3.70 (m, 1H), 2.44 (ddd, 1H, J= 2.44, 5.61 and 16.60 Hz), 2.32 (ddd, 1H, J= 2.93, 6.83 and 16.60 Hz), 2.05 (dd, 1H, J= 2.93 and 5.61 Hz) 1.20-1.80 (m, 14H), 0.87 (t, 3H, J=6.35 Hz); ^{13}C NMR ($CDCl_3$) δ 14.84, 23.31, 26.21, 27.95, 29.81, 30.09 (2C), 32.40, 36.74, 69.99, 70.83, 80.89; MS (FAB): m/z 182 (M, 2.3%), 165 (M, 15.8%), 159 (16.6), 154 (44.7), 141 (54.0), 137 (50.9), 117 (100.0), 97 (57.4), 95 (65.5), 91 (56.0).

1,2-Dodecadien-4-ol : ^{1}H NMR ($CDCl_3$) δ 5.25 (q, 1H, J= 6.35 Hz), 4.85 (m, 2H), 4.20 (m, 1H), 1.20-1.80 (m, 14H), 0.87 (t, 3H, J=6.35 Hz); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.65, 25.36, 29.24, 29.48, 29.53, 31.85, 37.50, 69.73, 77.45, 94.89, 206.95; IR (neat) 3350 (br, OH), 1953 (C=C=C) cm^{-1}; MS was not determined due to sample decomposition.

1-(1-Naphthyl)-3-butyn-1-ol: ^{1}H NMR ($CDCl_3$) δ 7.20 -8.30 (m, 7H), 5.67 (dd, 1H, J= 3.91 and 8.30 Hz), 2.90 (ddd, 1H, J= 2.93, 4.40 and 17.10 Hz), 2.76 (ddd, 1H, J= 2.93, 8.30 and 17.10 Hz), 2.15 (t, 1H, J= 2.93 Hz).

1-(1-Naphthyl)-2,3-butadien-1-ol: ^1H NMR ($CDCl_3$) δ 7.30 -8.20 (m, 7H), 6.00 (m, 1H), 5.60 (q, 1H, J= 6.35 Hz), 4.92 (m, 2H), 2.25 (s, 1H,); ^{13}C NMR and MS were not determined due to sample decomposition.

3-Phenyl-1,2-Dodecadien-4-ol : ^1H NMR ($CDCl_3$) δ 7.20 -7.50 (m, 5H), 5.25 (dd, 1H, J= 2.44 and 12.21 Hz), 5.22 (dd, 1H, J= 2.44 and 12.21 Hz), 4.62 (m, 1H), 1.80-1.10 (m, 14H); 0.87 (t, 3H, J=1.95 Hz); ^{13}C NMR ($CDCl_3$) δ 14.10, 22.66, 25.77, 29.24, 29.48, 29.55, 31.86, 36.30, 69.82, 80.64, 110.07, 126.77, 127.08, 128.56, 134.66, 207.03; IR (neat) 3350 (br, OH), 1953 (C=C=C) cm^{-1}; MS (EI): m/z 258 (M, 10. 4%), 146 (.43.3), 117 (33.6), 116 (100), 115 (52.9),105 (12.0), 77 (6.0), 69 (14.4), 55 (11.8).

3-Phenyl-2,3-butadien-4-ol : ^1H NMR ($CDCl_3$) δ 7.20 -7.50 (m, 5H), 5.25 (s, 2H), 4.60 (2, 2H), 1.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 61.50, 80.29, 105.95, 126.10, 127.19, 128.62, 133.75, 207.54; IR (neat) 3350 (br, OH), 1953 (C=C=C) cm^{-1}; MS (FAB): m/z 147 (M + 1, 13.4%), 146 (M, 8.7%), 129 (26.0), 117 (19.4), 115 (49.1), 105 (100.0), 91 (41.3).

3-Phenyl-1,2-decadien-5-yn-4-ol : ^1H NMR ($CDCl_3$) δ 7.20 -7.60 (m, 5H), 5.32 (s, 1H), 5.31 (s, 2H), 2.22 (t,d, 2H, J= 1.95 and 6.84 Hz), 1.46 (m, 2H), 1.36 (m, 2H), 0.87 (t, 3H, J= 7.33 Hz); ^{13}C NMR ($CDCl_3$) δ 13.53, 18.42, 21.81, 30.49, 61.77, 79.18, 81.43, 87.19, 108.43, 126.84, 127.18, 128.39, 133.31, 207.39; IR (neat) 3350 (br, OH), 1955 (C=C=C) cm^{-1}; MS (EI): m/z 226 (M, 8.3%), 197 (22.8), 184 (18.7), 165 (11.3), 116 (100),115 (64.3), 111 (25.0), 105 (40.7), 77 (27.2).

E-1,4-Diphenyl-1,4,5-hexatrien-3-ol : ^{1}H NMR ($CDCl_3$) δ 7.10 -7.50 (m, 5H), 6.75 (d, 1H, J= 15.99 Hz), 6.41 (dd, 1H, J= 5.86 and 15.99 Hz), 5.30 (m, 3H), 2.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 70.65, 81.21, 109.14, 126.63, 126.83, 127.22, 127.77, 128.53, 128.57, 129.92, 131.32, 133.99, 136.58, 207.48; IR (neat) 3450 (br, OH), 1960 (C=C=C) cm^{-1}; MS (EI): m/z 248 (M, 4.5%), 106 (46.8), 105 (100), 86 (36.7), 84 (56.1), 77 (71.7), 51 (23.7).

1-(2-Furfuryl)-3-phenyl-2,3-butadien-1-ol : ^{1}H NMR ($CDCl_3$) δ 7.10 -7.50 (m, 6H), 6.30 (m, 2H), 5.73 (dt, 1H, J= 2.44 and 7.32 Hz), 5.38 (dd, 1H, J= 2.93 and 12.21 Hz), 5.32 (dd, 1H, J= 2.93 and12.21 Hz), 2.37 (d, 1H, J= 7.32 Hz); ^{13}C NMR ($CDCl_3$) δ 66.17, 82.04, 107.39, 107.85, 109.91, 125.96, 126.61, 127.86, 133.00, 141.62, 153.64, 205.81; IR (neat) 3350 (br, OH), 1955 (C=C=C) cm^{-1}; MS (EI): m/z 212 (M, 11.0%), 194 (13.7), 165 (17.1), 116 (100.0).

3-Methyl-1,2-dodecadien-4-ol : ^{1}H NMR ($CDCl_3$) δ 4.75 (m, 2H), 4.03 (m, 1H), 1.70(t, 3H, J= 3.02 Hz), 1.65-1.10 (m, 14H); 0.87 (t, 3H, J=1.95 Hz); ^{13}C NMR ($CDCl_3$) δ 14.81, 14.93, 23.28, 26.03, 29.81, 30.10 (2C), 32.38, 35.56, 72.59, 76.36, 101.65, 203.42; IR (neat) 3350 (br, OH), 1953 (C=C=C) cm^{-1}; MS (FAB): m/z 196 (M, 9.4%), 180 (10.9), 154 (97.6), 141 (38.8), 135 (100.0), 107 (63.3).

1-(1-Naphthyl)-2-methyl-2,3-butadien-1-ol: ^{1}H NMR ($CDCl_3$) δ 7.30 - 8.30 (m, 7H), 5.87 (m, 1H), 4.92 (m, 2H), 2.50 (d, OH, J= 3.91 Hz), 1.63 (t, 3H, J=3.09 Hz); ^{13}C NMR ($CDCl_3$) δ 15.29, 72.35, 77.29, 101.71, 123.22, 123.68, 124.53, 124.86, 125.30, 127.72, 128.03, 130.27, 133.14, 136.14, 204.13; MS (FAB) m/z 210 (M, 17.5 %), 193 (100.0), 178 (22.7), 165 (13.4), 157 (28.2), 129 (17.3).

1-Phenyl-2-trimethylsilyl-2,3-butadien-1-ol: ^{1}H NMR ($CDCl_3$) δ 7.20 - 7.40 (m, 5H), 5.25 (s, 1H), 4.76 (m, 2H), 2.3 (s, OH), -0.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ -1.19, 72.91, 71.97 (2C), 101.68, 126.96, 127.80, 128.28, 143.02, 206.99; IR (neat) 3350 (br, OH), 1953 (C=C=C) cm^{-1}. [14]

3-Trimethylsilyl-1,2-dodecadien-4-ol : ^{1}H NMR ($CDCl_3$) δ 4.55 (m, 2H), 4.15 (br, 1H), 1.10-1.40 (m, 14H); 0.87 (t, 3H, J=1.95 Hz), 0.15 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ -0.88, 14.10, 22.66, 25.61, 29.26, 29.51, 29.59, 31.87, 37.94, 70.67, 71.84, 101.70, 207.19; IR (neat) 3350 (br, OH), 1953 (C=C=C) cm^{-1}.[14]

1-(1-Naphthyl)-2-phenyldimethylsilyl-2,3-butadien-1-ol: ^{1}H NMR ($CDCl_3$) δ 7.20 -8.00 (m, 12H), 5.85 (d, 1H, J= 2.93 Hz), 4.61 (dd, 1H, J= 2.93 and 11.72 Hz), 4.56 (dd, 1H, J= 2.93 and 11.72 Hz), 2.10 (br, OH) 0.33 (s, 3H), 0.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ -2.89, -2.52, 71.06, 72.88, 99.90, 124.12, 124.77, 124.91, 125.37, 125.76, 127.70, 128.46, 128.57, 129.20, 130.96, 133.82, 133.84, 137.22, 137.92, 209.05; IR (neat) 3600-3400 (br, OH), 1950 (C=C=C) cm^{-1}; MS (FAB) m/z 330 (M, 1.3 %), 313 (33.8), 157 (63.7), 135 (100.0).

1-Isopropyl-2-phenyldimethylsilyl-2,3-butadien-1-ol: ^{1}H NMR ($CDCl_3$) δ 7.30 -7.70 (m, 5H), 4.61 (dd, 1H, J= 2.44 and 11.23 Hz), 4.57 (dd, 1H, J= 2.44 and 11.23 Hz), 3.87 (dt, 1H, J= 2.44 and 5.37 Hz), 1.70 (m, 1H); 0.86 (d, 3H, J=6.34 Hz), 0.81 (d, 3H, J= 6.34 Hz), 0.43 (s, 3H), 0.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ -2.57, -2.36, 16.08, 19.97, 33.49, 72.10, 75.52, 98.84, 127.84, 129.24, 133.81, 137.83, 208.32; IR (neat) 3600-3400 (br, OH), 1950 (C=C=C) cm^{-1}; MS (CI): m/z

264 (M + NH_4^+ 0.4%), 246 (M, 3.8), 229 (36.7), 207 (20.2), 174 (17.3), 152 (39.5), 137 (25.8), 135 (100.0).

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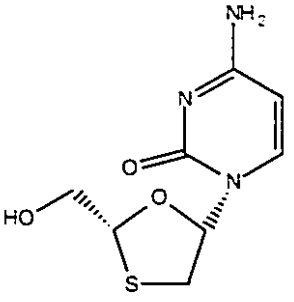
Chapter 4

Indium-mediated coupling of Aldoses with γ -Substituted Allyl Bromides in Aqueous Media. Stereoselective Generation of Two New Contiguous Stereogenic Centres in the Synthesis of Novel Carbohydrates.

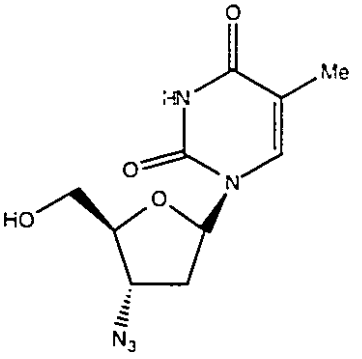
4.1 Introduction

Carbohydrates are amongst the most ubiquitous compounds in nature. They are used as sources of energy, means of storing energy, and as parts of macromolecules either to modify properties, as in glycoprotein or as building blocks such as in DNA and RNA. Synthetic organic chemists have found carbohydrates a valuable source of chiral centres for incorporation into a synthetic target. In this context, many of the reactions discovered by the early carbohydrate chemists are still invaluable as extensive modification of the carbohydrate may be required before it can be incorporated into the synthetic sequence. An expansion of the 'chiral pool' would do much to alleviate this problem, as only a few monosaccharides are readily available from natural source.

Many biologically important molecules contain carbohydrate units, and the synthesis of modified analogues for biological activity testing is often tedious. In both the traditional synthetic organic and medicinal chemistry fields, it is advantageous to have useful synthetic methods to carbohydrate analogues. The preparation of analogues such as (-)-2'-deoxy-3'-thiacytidine (3TC) **4.0a** and 3'-azido-2',3'-deoxythymidine (AZT) **4.0b**,[1] which in combination therapy is showing significant promise for the treatment of AIDS, admirably illustrates this point.[2]

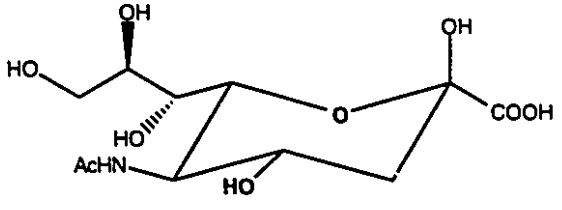


4.0a

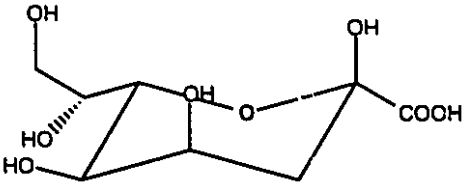


4.0b

The increasing awareness of the important biological role of carbohydrates has recently stimulated renewed interest in the synthesis of natural and unnatural sugars. The so called 'higher sugars' constitute an interesting family of monosaccharides. For example, the carbohydrates on the surface of cells play a central role in cellular recognition events.[3] Sialic acid **4.1** (N-acetylneuraminic acid), an element of gangliosides,[4] sialyl Lewis x,[5] and many other glycoconjugates,[6] is arguably the most important of these critical mediators of intracellular and cell-virion recognition.[7]



4.1



4.2

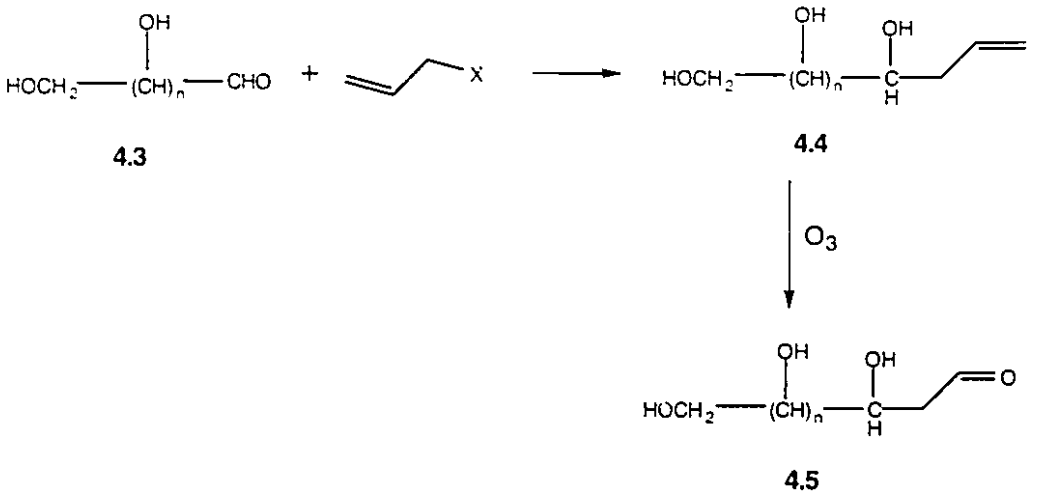
Another case in point is the monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid **4.2** (KDO), an integral component of the lipopolysaccharides of Gram-negative bacteria. New syntheses of KDO may be useful in developing

analogues capable of disrupting the biosynthesis of bacterial cell-wall components, and thereby lead to new antibacterial agents.[8]

Despite the plethora of synthetic approaches to sialic acids[9] and KDO,[10] carbohydrate synthesis lacks a repertoire of efficient and versatile C-C bond forming reactions that can be carried out on unprotected carbohydrates in aqueous media. The convenient and efficient indium-mediated allylation method for extending the carbon chain of unprotected carbohydrates has recently been developed by us[11] and others[12] and its application has been effectively demonstrated in the synthesis of a number of 2-deoxyaldoses. In its modified form, the indium-mediated protocol in aqueous media has been applied to a concise synthesis of N-acetylneuraminic acid (sialic acid).[13]

4.2 Indium-mediated allylation of aldoses aqueous media: the issue of diastereoselectivity

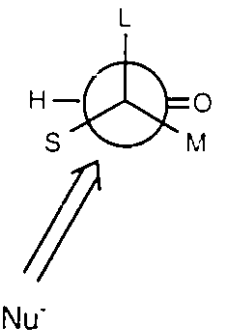
In its most general form, the synthesis of higher carbohydrates can be illustrated by scheme 4.1. The coupling of an aldose **4.3** with an allylic halide in aqueous media is mediated by a metal to give the coupled product **4.4**. Indium has been found to be the metal of choice in effecting the coupling reaction. The terminal double bond is then ozonised to generate a new aldehyde function. The overall sequence is therefore a two carbon homologation to give the 2-deoxy aldose **4.5**.



Scheme 4.1

In the coupling step giving rise to compound **4.4**, and then to the new carbohydrate **4.5**, a new stereogenic center is created, adjacent to an existing chiral center bearing a hydroxy function. With indium-mediated coupling, the stereoselectivity has been found to give generally syn-selectivity. The syn/anti isomeric ratio in **4.4** and thus **4.5** ranged between 3:1 to 6:1.[12a] The configuration at the new stereogenic center of the product homoallylic alcohol was unambiguously assigned by transforming the adducts **4.4**, obtained from aldoses such as D-arabinose, D-ribose and D-glucose to the corresponding peracetylated heptose and octose.

The addition of allyl anion equivalents such as allylindium reagents to the carbonyl group of aldoses has been shown to be diastereoselective. This stereoselectivity has been explained using the Felkin-Anh model which shows that the trajectory of the nucleophile is at an angle to the carbonyl plane (Fig 4.1). The major shortfall of the model centres around identification of the 'large' group. Interpretation of the Felkin-Anh model also gives powerful insights into means to optimize asymmetric induction.[14]



S = small substituent
M = medium substituent
L = Large substituent

Fig 4.1

Nonetheless, chelation controlled addition is believed to be operative in the nucleophilic addition to aldoses due to the prevalence of hydroxy groups. Although chelation-controlled addition can be accomplished with a wide variety of substrates, it is simplest to consider the rules by use of the models developed for α-substituted carbonyl compounds. The chelation model of Cram (Fig. 4.2), where formation of the chelate can reverse the stereochemical outcome of the reaction compared to when a chelate is not formed, has been widely used to account for observed stereoselectivities.[15]

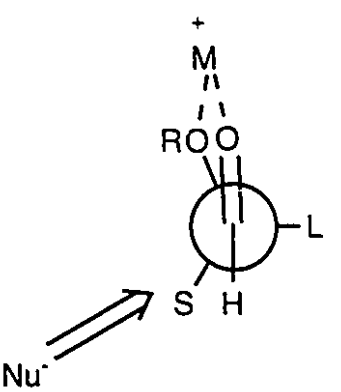
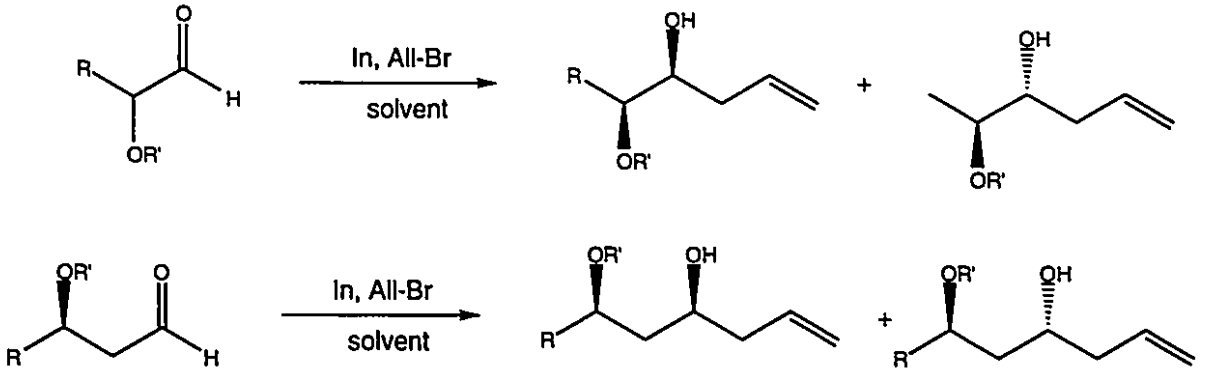


Fig 4.2

The stereochemical course of the indium-promoted allylations to α- and β- oxy aldehydes has been investigated by Paquette *et al.* in solvents ranging

from anhydrous THF to pure H_2O (see Table 4.1).[16] The free hydroxyl derivatives react with excellent diastereofacial control to give significantly heightened levels of the syn-1,2-diols (α-series) and anti-1,3-diol (β-series) (Scheme 4.2). Relative reactivities were determined in the α-series and the hydroxy aldehyde proves to be the most reactive substrates. The reactivity ordering seems to suggest that



R'= TBS, Bn, H

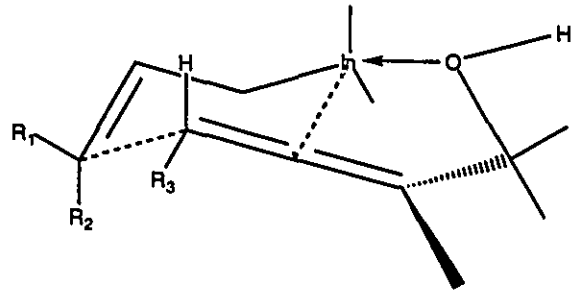
Scheme 4.2

the diastereoselectivity stems from chelated intermediate. The rate acceleration observed in water can be heightened by initial acidification. Indeed, the indium-promoted allylation reaction mixtures become increasingly acidic on their own.

When α- and β- alkoxy carbonyl compounds are involved and chelate intermediates intervene, mechanistic analysis is simplified. In such instances, nucleophilic addition often occurs from the sterically less demanding π-face of the preorganised complex.[17] Grignard reagents are renowned to be particularly well suited to Cram-type chelate-control,[18] while non-chelate behavior has been reported for organolithium,[19] alkyltitanium[17] and allylchromium[20] reagents.

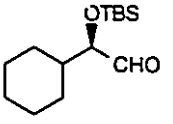
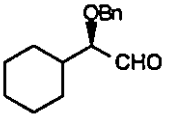
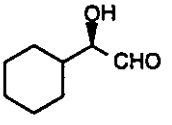
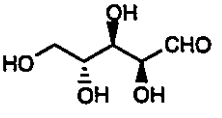
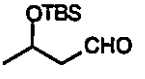
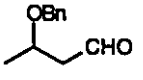
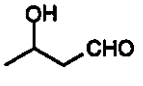
The sensitivity of the above organometallic reagents to moisture requires that their addition reaction be performed in anhydrous organic solvents. The

metal indium has been shown to offer intriguing advantages for effecting C-C bond construction in an aqueous environment. The Cram and Felkin-Anh proposals have not been verified on reactions carried out in water or under 'wet conditions' of any type. This change to a significantly more polar hydrogen bonding medium could conceivably damp those factors controlling facial selectivity in the absence of water. However, if coordination to indium overrides those solvation forces that would break down the chelate, then the Cram and Felkin-Anh proposals may still apply.[16] This intrinsic ability of indium to chelate to hydroxyl functions was recently demonstrated by Butsugan et al in the regioselective allylindation of α-allenic alcohols. The allylindation is a carbometallation reaction in which an allylindium species is added to the unsaturated system of an alkynols or an allenic alchohols. Allylic indium sesquihalides, prepared from indium powder and allylic halides in DMF, are treated with the allenic or alkynic alcohols. No reaction occurs at room temperature, but at elevated temperatures (100-140°C) clean allylindation occurs. The coupling occurs regioselectively at the γ-terminus of the allylindium reagent. In addition, a hydroxyl group in close proximity to the unsaturated unit is essential for smooth allylindation (Scheme 4.3).[21] Masking the hydroxyl group of the α-allenic alcohols completely inhibits allylindation.



Scheme 4.3

Table 4.1: Indium mediated allylation of α- and β- oxy aldehydes in various solvent

Entry	Carbonyl Compounds	Solvent	Reaction Time (h)	syn :	anti	Yield (%)
1		H_2O	3.5	1	3.9	90
2		H_2O-THF (1:1)	2.5	1	4.2	87
3		THF	10	1	4.3	90
4		H_2O	3	1	1.2	92
5		H_2O-THF (1:1)	2.5	1	2.2	93
6		THF	40-47	1	3.9	87
7		H_2O	3.5	9.8	1	85-90
8		H_2O	24-30	10.2	1	90
9		THF	50-76	3.0	1	87
10		H_2O	3.5	1	1	84
11		H_2O-THF (1:1)	3.5	1.2	1	87
12		THF	8.5	1.7	1	77
13		H_2O	2.5	1	1	80
14		H_2O-THF (1:1)	2.7	1	1	84
15		THF	40-47	1	3.9	77
16		H_2O	2	1	8.5	77
17		H_2O-THF (1:1)	2	1	8.2	74
18		THF		No reaction		

In brief, the addition of the allylindium reagent to α- and β- hydroxy aldehydes in water have been demonstrated to be highly diastereoselective.

The free hydroxyl derivatives, which were much more reactive than the corresponding protected substrates such as TBS and benzyl derivatives, conformed expectedly to chelation-controlled addition (Table 4.1). The ability of the indium to conformationally lock the carbonyl substrate prior to nucleophilic attack is indicative that coordination to the substrate can indeed overcome the water solvation forces, especially when the neighboring functionality is an unprotected hydroxyl substituent such as an aldose.

The sense of asymmetric induction in the α-hydroxy carbonyl compounds, viz a strong kinetic preference for the formation of the syn-1,2-diols, is consistent with the operation of the classic Cram model as in Fig. 4.3. Once complexation occurs, the allyl group is transferred to the carbonyl carbon from the less hindered π-face opposite to that occupied by the R group.

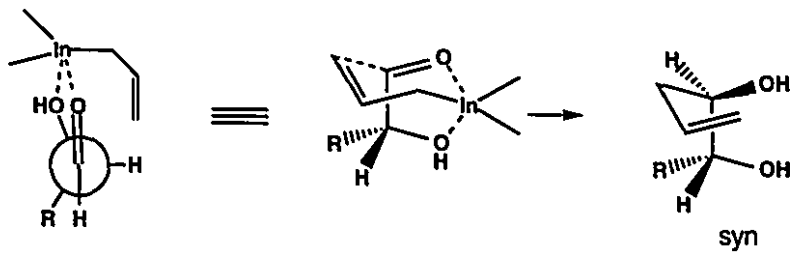


Fig 4.3

For the β-chelate reactions, the factors that influence product formation appear to be the same. Intramolecular attack is guided to occur syn to the preexisting hydroxyl. The reaction trajectory leads preferentially to the anti diol Fig 4.4.

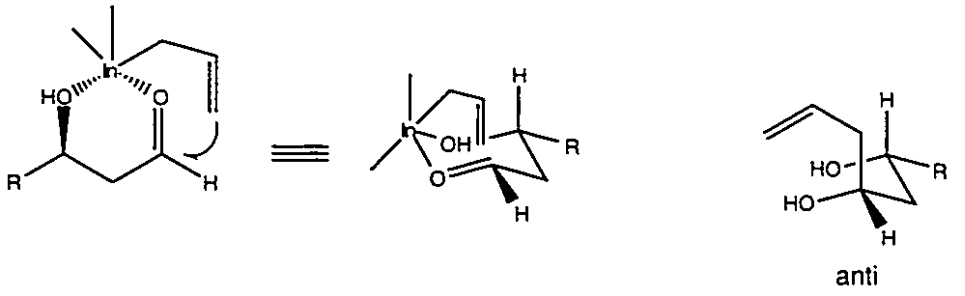
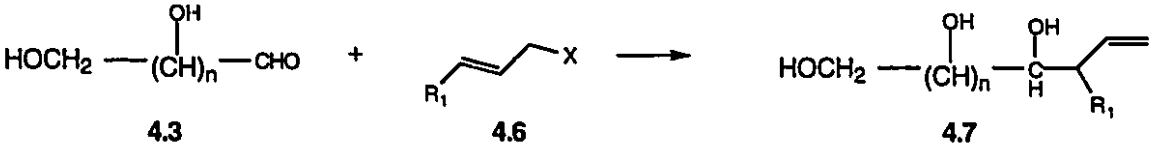


Fig 4.4

With the above information in hand, along with our previous findings that γ-substituted allyl halides reacted with carbonyl compounds in a regio- and diastereoselective manner, we proceeded to investigate the indium mediated coupling of aldoses with γ-substituted allyl halides in water as solvent.

4.3 Regio- and Stereoselective coupling of aldoses in aqueous media: Synthesis of 2-deoxy-2-substituted aldoses.

The synthesis of higher carbohydrates to include 2-deoxy-2-substituted aldoses by using γ-substituted allylic halides (**4.6**) as the starting component, would be a significant extension of the aqueous indium-mediated methodology. In such a synthesis (scheme 4.4), two new stereogenic centers will be generated in the coupling step giving **4.7**. What is the likely stereochemical outcome of such a reaction?

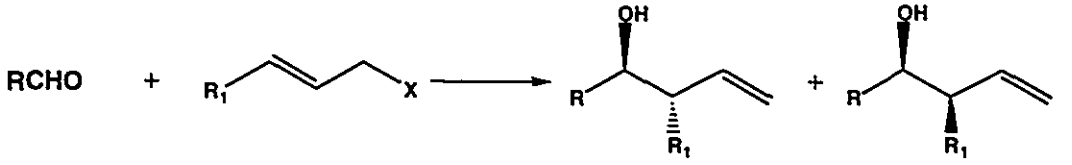


4.3 **4.6** **4.7**

Scheme 4.4

One piece of information that has been independently examined is the stereochemistry of the indium-mediated coupling of simple aldehydes **4.8** with

γ-substituted allylic halides **4.6**. We have found that, in all cases, anti-selectivity was obtained for product **4.9** (scheme 4.5),[22,23] An example is the coupling of iso-butyraldehyde (**4.8**, R=i-Pr) with E-cinnamyl bromide (**4.6a**, R_1=Ph) which gives stereoselectively the anti-product **4.9a** in good yield. One might reasonably expect, therefore, combining these two observations, that the syn, anti isomer would be the preferred product in **4.7**.

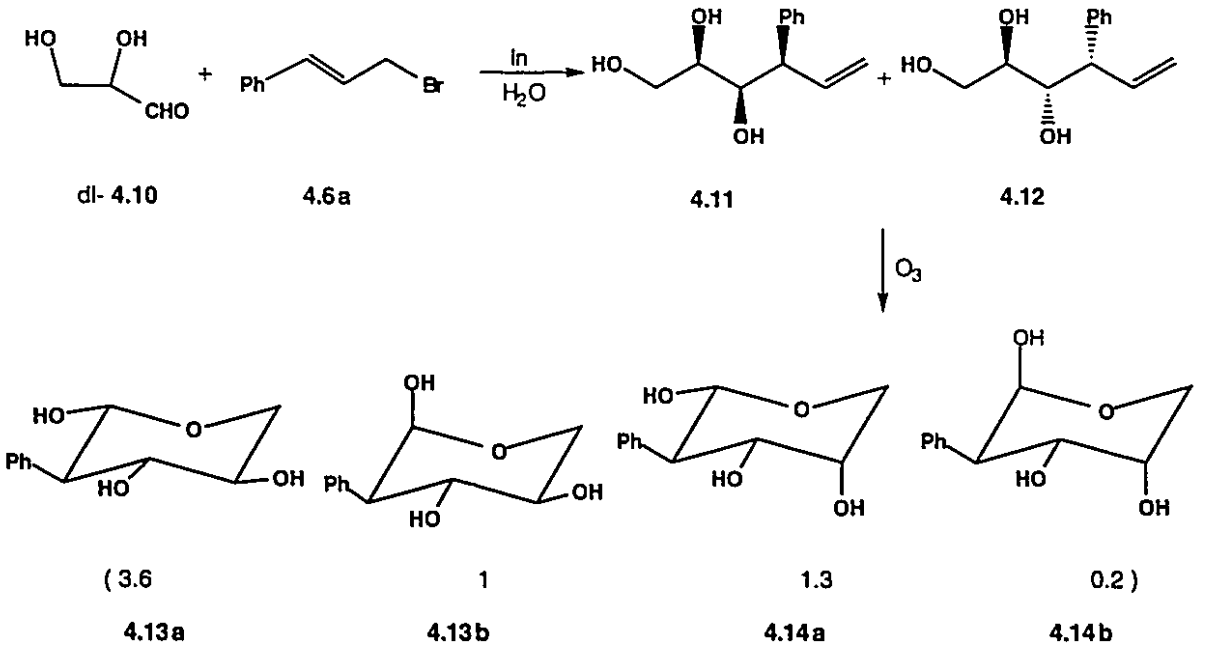


4.8 **4.6** **4.9a** **4.9b**

Scheme 4.5

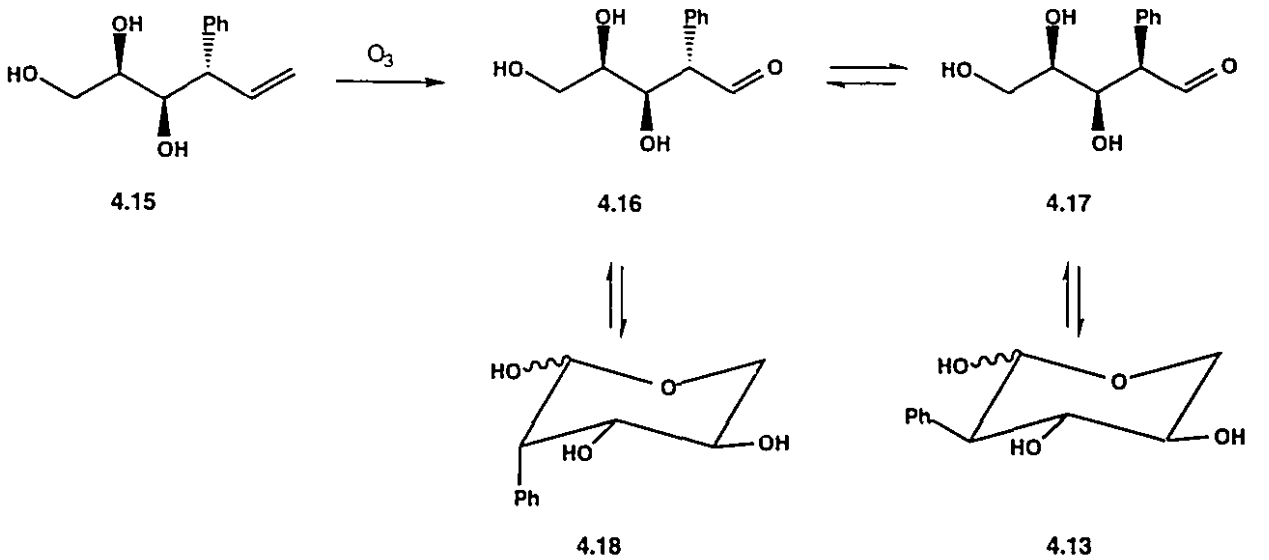
(1) **Synthesis of 2-deoxy-2-phenylaldoses**. We began by examining the reaction of glyceraldehyde (**4.10**) with E-cinnamyl bromide (**4.6a**) mediated by indium in water. The reaction gave in good yield the coupled product which by nmr was found to be a mixture of two diastereoisomers (**4.11** and **4.12**) in a ratio of 2 : 1. Ozonolysis of **4.11/4.12** (purified to have **4.11/4.12** in a ratio of 3:1) gave the 2-deoxy-2-phenylpentoses **4.13** and **4.14** as pyranoses. Careful nmr analysis of the product indicated it to be a mixture of four isomers in a ratio of 3.6:1:1.3:0.2 (Scheme 4.6, only one of both enantiomeric forms is presented). Using 2D-homo and hetero NMR spectroscopy, it was possible to establish that **4.13a** and **4.13b** are anomers corresponding to the precursor **4.11**, whereas **4.14a** and **4.14b** are anomers derived from **4.12**. What is puzzling is the fact that the major isomer **4.13** has the stereochemistry indicated with the hydroxy groups and the phenyl group equatorial. This means in turn that **4.11** has the

syn, syn stereochemistry. Futhermore, the minor isomer **4.14**, and in turn the precursor **4.12**, has the anti, syn stereochemistry.



Scheme 4.6

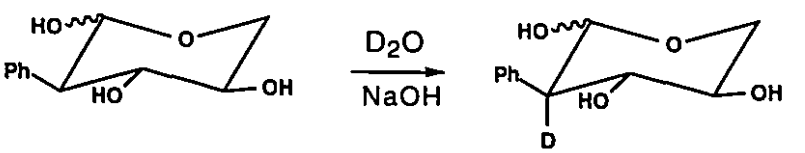
One possible explanation for the formation of the stereoisomer **4.13** is that the carbon centre bearing the phenyl group in **4.13** is easily epimerisable. Even though the coupling step gives the expected syn, anti product **4.15**, the ozonolysis product **4.16** is epimerised under the reaction conditions to give **4.17** which is thermodynamically more stable in the pyranose form (Scheme 4.7, again only one of the two enantiomer is presented). When **4.13** was treated with D_2O and NaOH for a long time, deuterium incorporation was indeed observed at the C-2 position to give **4.19** according to scheme 4.8. However, the epimerisation required the strong basic conditions. Indeed, quenching the ozonolysis mixture with D_2O did not lead to deuterium incorporation in **4.13**. We therefore consider the epimerization mechanism to be an inadequate explanation for the formation of **4.13**.



4.15 4.16 4.17

4.18 4.13

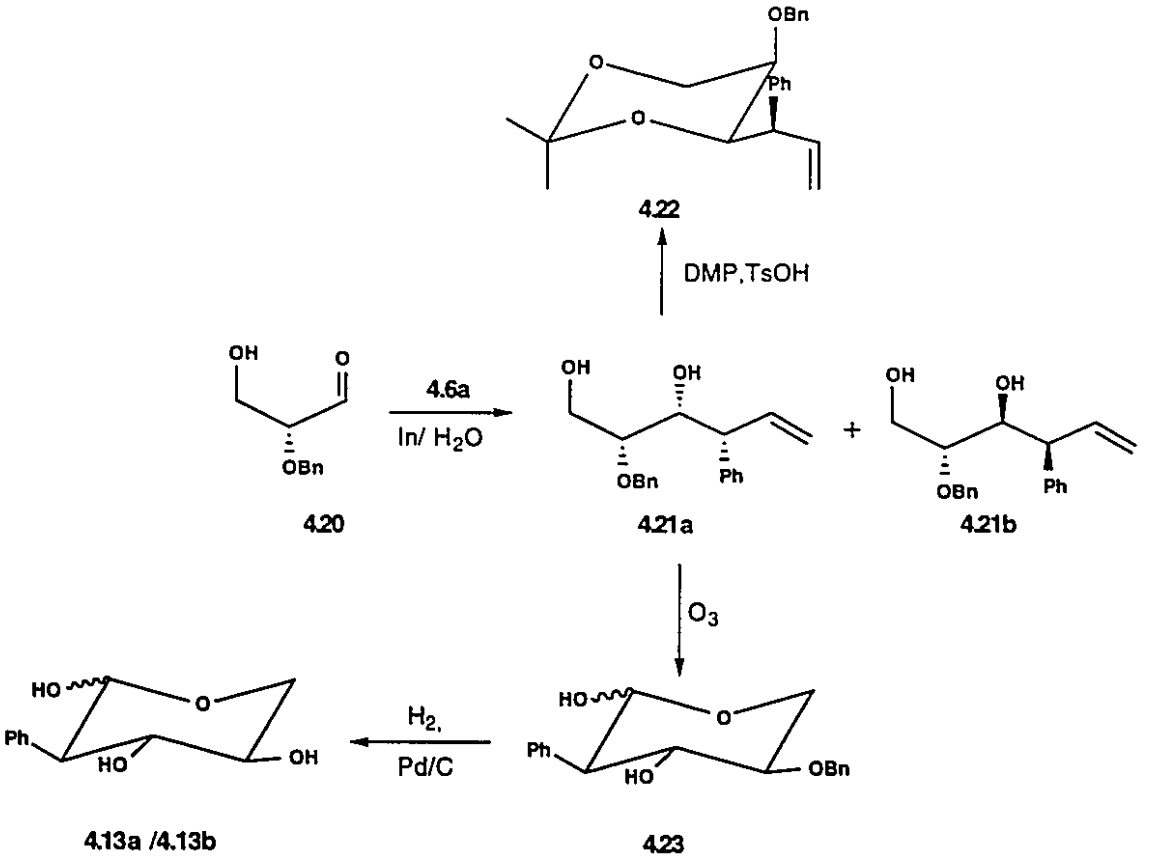
Scheme 4.7



4.13 4.19

Scheme 4.8

To further secure the structure of **4.13**, The following studies were carried out. (R)-2-O-Benzylglyceraldehyde **4.20**, prepared from diethyl (+)-tartrate,[24] was coupled with E-cinnamyl bromide (**4.6a**) and indium in water to give the coupled product **4.21** with high stereoselectivity (**4.21a**:**4.21b**=10:1) (Scheme 4.9).



Scheme 4.9

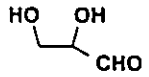
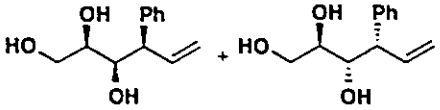
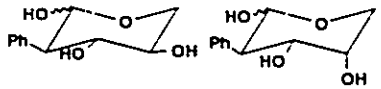
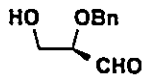
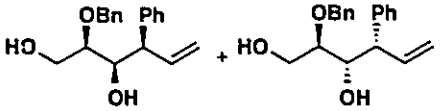
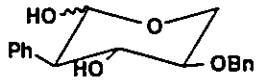
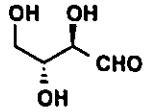
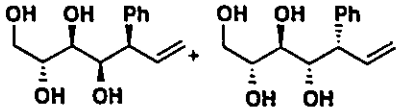
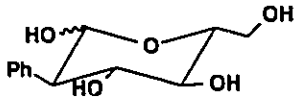
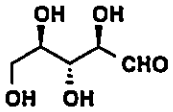
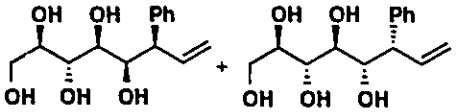
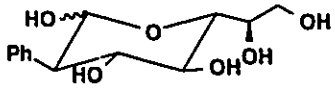
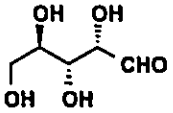
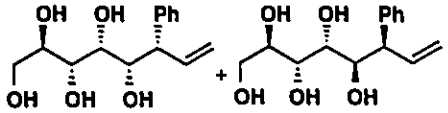
The major isomer **4.21a** was acetalized with dimethoxypropane (DMP) under acidic conditions to give the crystalline acetonide **4.22**. The stereochemistry of **4.22** was deduced unambiguously by X-ray structure determination (Fig 4.5, see Appendix). This shows clearly that the coupling step gave the syn, syn stereochemistry for **4.21a**. Compound **4.21a** on ozonolysis gave the benzylated 2-deoxy-2-phenylpentose **4.23** which existed according to nmr in the pyranose form as a mixture of anomers **4.23a** and **4.23b** in a ratio of 1:1 in $CDCl_3$. Interestingly, the α-anomer **4.23a** could be crystallized out. When dissolved in $CDCl_3$, **4.23a** slowly anomerized and achieved equilibrium in 24hrs. Hydrogenolysis of **4.23** with Pd on charcoal and hydrogen gave

compound **4.13**, thus confirming the stereochemical assignment previously based solely on nmr analysis.

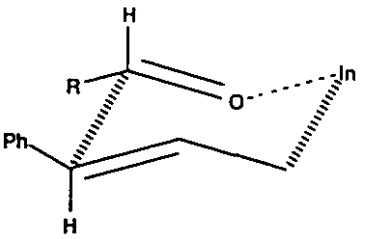
Other aldoses reacted with E-cinnamyl bromide (**4.6a**) in a similar manner to give the coupled products as a mixture of two diastereomers with the syn, syn stereochemistry for the major isomer and the anti, syn stereochemistry for the minor isomer (entries 3-5, Table 4.1). Thus, starting from D-erythrose (**4.24**), the coupled products **4.25** and **4.26** were obtained in a ratio of 2:1 in 87% yield. Ozonolysis of the major isomer **4.25** gave 2-deoxy-2-phenylglucopyranose **4.27** as a mixture of α- and β-anomers with the β-isomer predominating (α:β=1:6.7). Similarly, coupling of E-cinnamyl bromide (**4.6a**) with D-ribose (**4.28**) with indium in water gave two diastereomers **4.29** and **4.30** in a ratio of 2.4 to 1. Again, the major isomer **4.29** was ozonized to the 2-deoxy-2-phenyl-heptaldose **4.31** which existed according to NMR in the pyranose forms. Finally, D-arabinose (**4.32**) was also coupled with **4.6a** to give two diastereomers **4.33** and **4.34** in a ratio of 3.8 to 1, albeit in an unoptimised yield of 43%. Even though the relative stereochemistry of **4.33/4.34** has not been rigorously established by ozonolysis to the pyranose, the similar coupling constants exhibited by **4.33/4.34** in the nmr spectrum in comparison to similar compounds left little doubt that the same stereochemical course was followed in this coupling reaction as well.

At this point, it is necessary to comment on the stereoselectivity of the coupling reaction. While the relative preference of syn stereochemistry of the newly generated stereogenic centre bearing the hydroxy group (referred to as Cβ for convenience) with reference to the existing chiral centre bearing the α-hydroxy group (referred to as Cγ) is not unexpected, it is somewhat surprising to

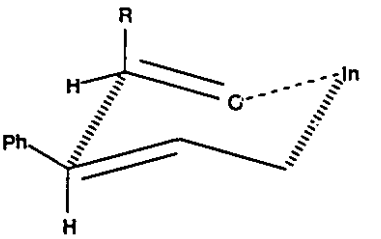
Table 4.2: Indium mediated coupling of aldoses with E-Cinnamyl bromide (4.6a)

Entry	Aldose	Product (% yield)	Ozonolysis (% yield)
1	 **4.10**	 **4.11** (2 : 1) **4.12** (65)	 **12a/12b** **13a/13b** (75)
2	 **4.20**	 **4.21a** (10 : 1) **4.21b** (83)	 **4.23** (84)
3	 **4.24**	 **4.25** (2 : 1) **4.26** (87)	 **4.27** (98)
4	 **4.28**	 **4.29** (2.4 : 1) **4.30** (83)	 **4.31** (87)
5	 **4.35**	 **4.33** (3.8 : 1) **4.34** (83)	

find the newly generated stereogenic centre bearing the phenyl group (referred to as Cα) to be syn exclusively with reference to Cβ. In the indium mediated coupling of cinnamyl bromide (E or Z) with iso-butyraldehyde, the relative anti-preference (Cα and Cβ) was explained by the two chair transition states **4.35a** and **4.35b** in which **4.35a** is preferred over **4.35b**.[23]

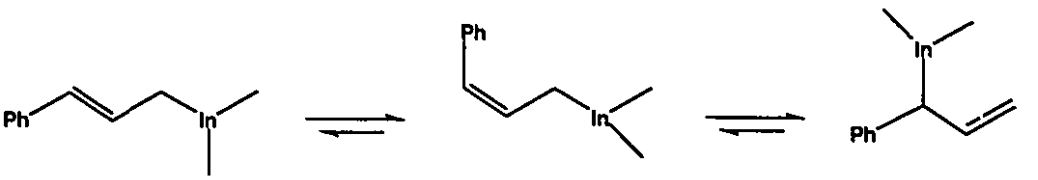


4.35a



4.35b

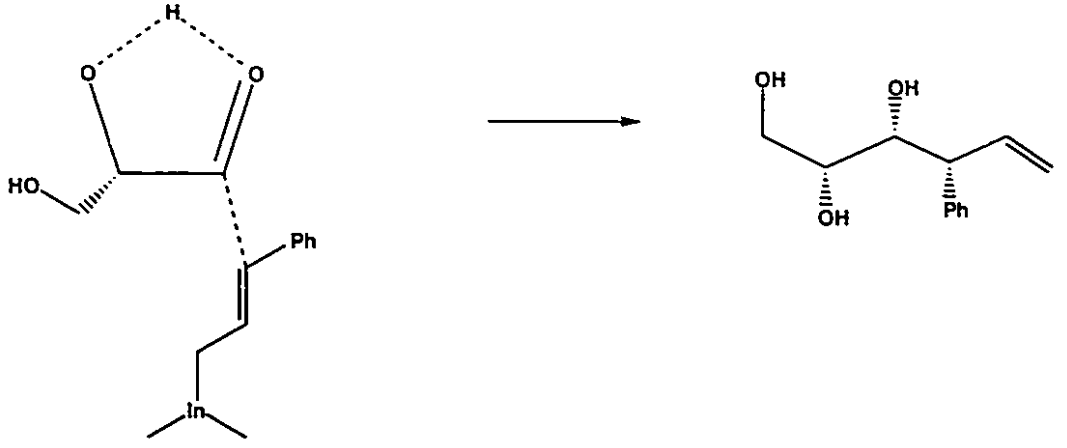
Furthermore, the cinnamylindium species assumed the preferred transoid stereochemistry (**4.36a**) even though a dynamic equilibrium presumably exist between it, the cisoid isomer (**4.36b**) and the α-regioisomer (**4.36c**). Alternative explanations will have to be offered to account for the change in stereochemistry in the coupling of **4.6a** with aldoses. Two possibilities come to mind. The first possibility is that for the α-hydroxyaldehydes, the cyclic transition state exemplified by **4.35** is no longer operative because the carbonyl function



4.36a 4.36b 4.36c

is now hydrogen bonded with the adjacent hydroxy group. The cinnamylindium species (**4.36a**) approaches the carbonyl function in an acyclic fashion as illustrated in **4.37** (Scheme 4.10). The Cγ-Cβ syn selectivity is governed by π-face selectivity with the cinnamylindium species coming from the less hindered side. The Cβ-Cα syn selectivity is governed by the preference of the phenyl

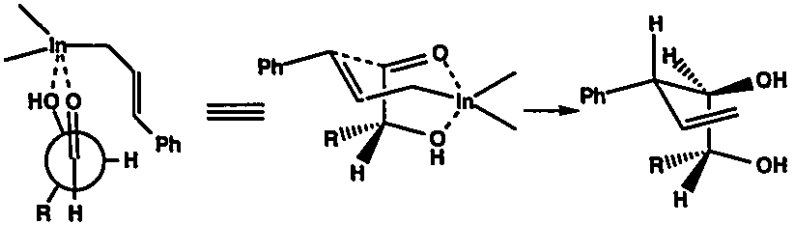
substituent to be away from the aldehyde substituent. The second possibility is that the cinnamylindium species **4.36a**, in addition to coordination with the



4.37

Scheme 4.10

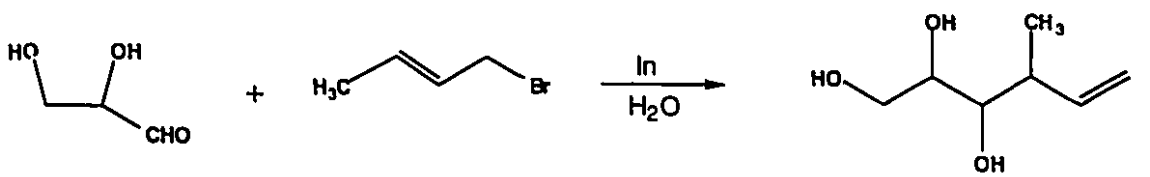
carbonyl oxygen, is also chelated with the adjacent hydroxy function as illustrated in **4.38a** and **4.38b** (scheme 4.11). In this case the syn syn stereochemistry would be favoured. The Cγ-Cβ syn selectivity is governed by π-face selectivity from the less hindered side. The Cβ-Cα syn stereochemistry is controlled by the geometry of the cinnamylindium species. The fact that the (R)-2-O-benzylglyceraldehyde (**4.20**) reacted with **4.6a** to give the highly stereoselective syn syn adduct **4.21a** suggest that the second possibility is more compatible with these results.



4.38a **4.38b** **syn, syn**

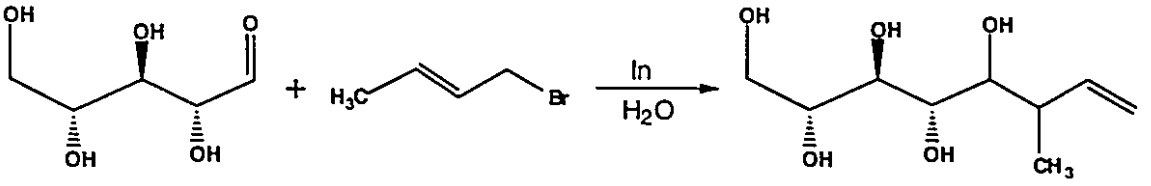
Scheme 4.11

(2) **Indium mediated coupling of aldoses with crotyl bromide (4.6b)**. One would expect that the crotylindium species derived from crotyl bromide (**4.6b**) to be an equilibrium mixture of cisoid and transoid structure.[25] In the indium mediated coupling of simple aldehydes with crotyl bromide, a 1:1 mixture of anti/syn diastereomers were usually obtained. We found that when crotyl bromide (**4.6b**) was coupled to (dl)-glyceraldehyde by indium in water, the coupled product was a mixture of four diastereomers, presumably (syn, syn) **4.39**, (anti, syn) **4.40**, (syn, anti) **4.41**, and (anti, anti) **4.42**, from both proton and carbon NMR spectroscopy (Scheme 4.12). Similarly, when crotyl bromide was coupled to D-ribose, the product obtained was a mixture of four diastereomers (**4.43-4.46**) as well (Scheme 4.13). The reaction therefore is not that useful as a way to synthesize stereoselectively 2-deoxy-2-methylaldoses. The lack of stereoselectivity is also in line with the indium chelation mechanism in that the crotylindium species can attack the carbonyl group in either the cisoid or transoid structure as in **4.47a** and **4.47b**.



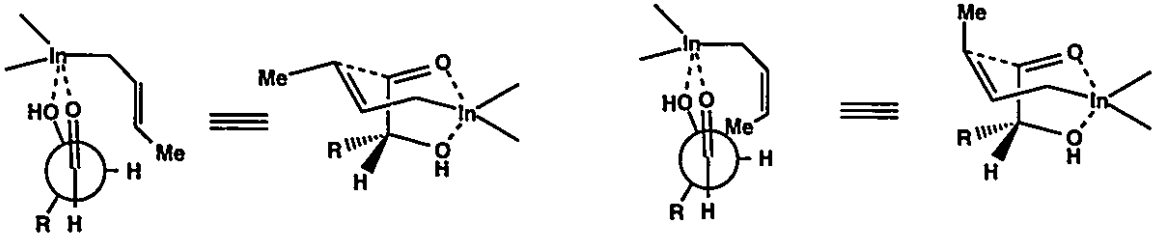
4.6b **4.39-4.42**

Scheme 4.12



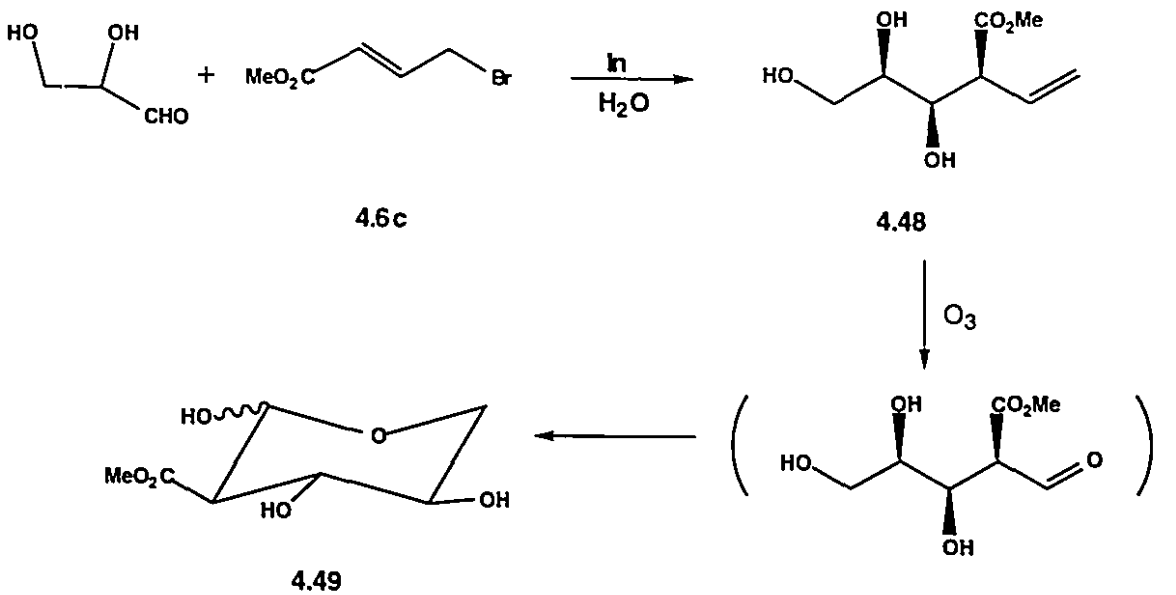
4.6b 4.43-4.46

Scheme 4.13



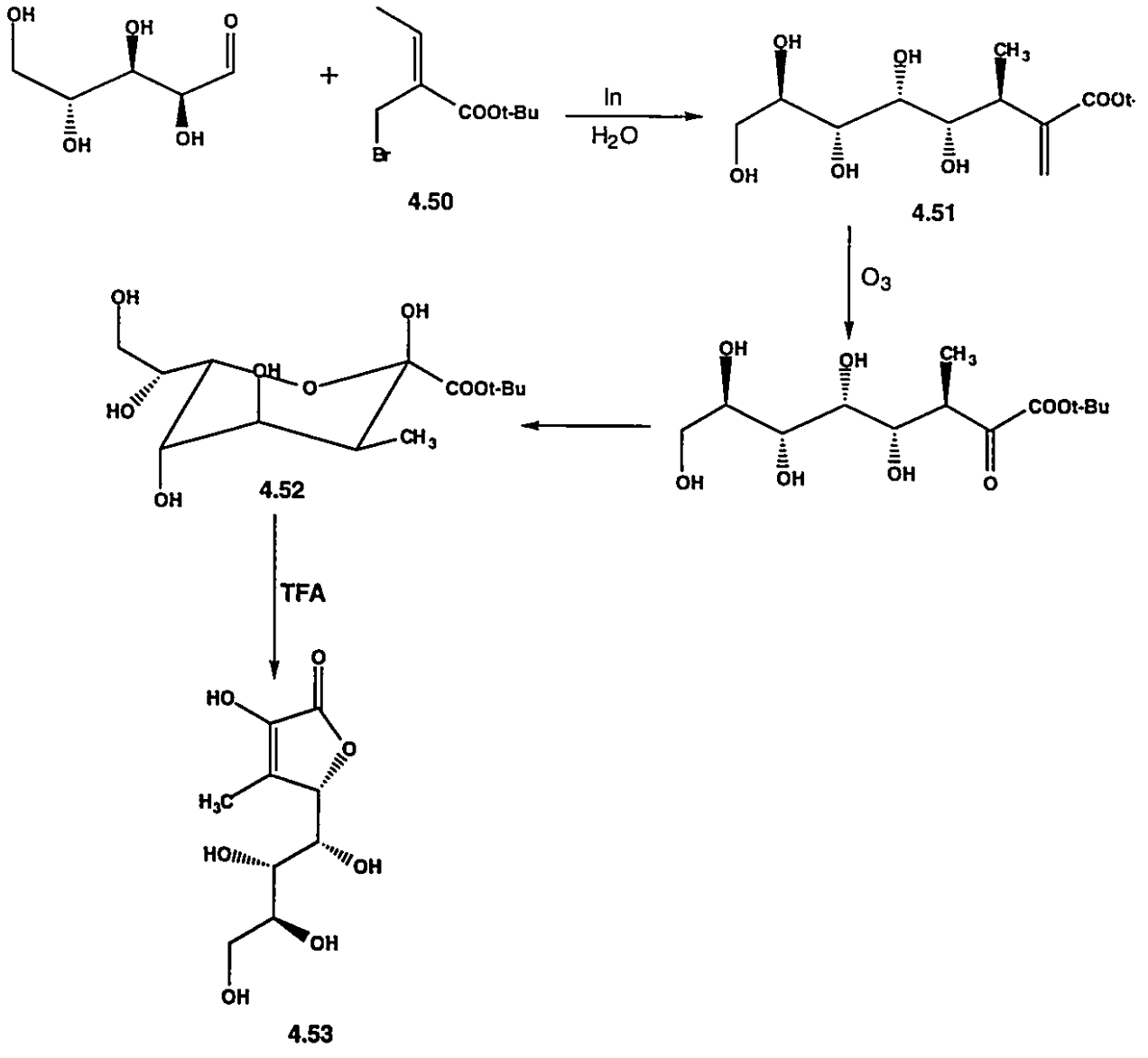
4.47a 4.47b

(3) **Synthesis of 2-deoxy-2-methoxycarbonylpentose.** On the other hand , one would expect the indium species derived from bromocrotonate to retain the transoid geometry. Indeed, when methyl bromo-E-crotonate (**4.6c**) was coupled to (dl) -glyceraldehyde with indium in water, the product **4.48** was found to be one diastereomer (one enantiomer represented). It is assigned the syn,syn stereochemistry. The stereochemistry was confirmed when **4.48** was ozonised to pentose **4.49**. Proton NMR spectroscopy of **4.49** was consistent with the relative stereochemistry of all the substituents and the pyranose structure with the β-anomer predominating (Scheme 4.14).



Scheme 4.14

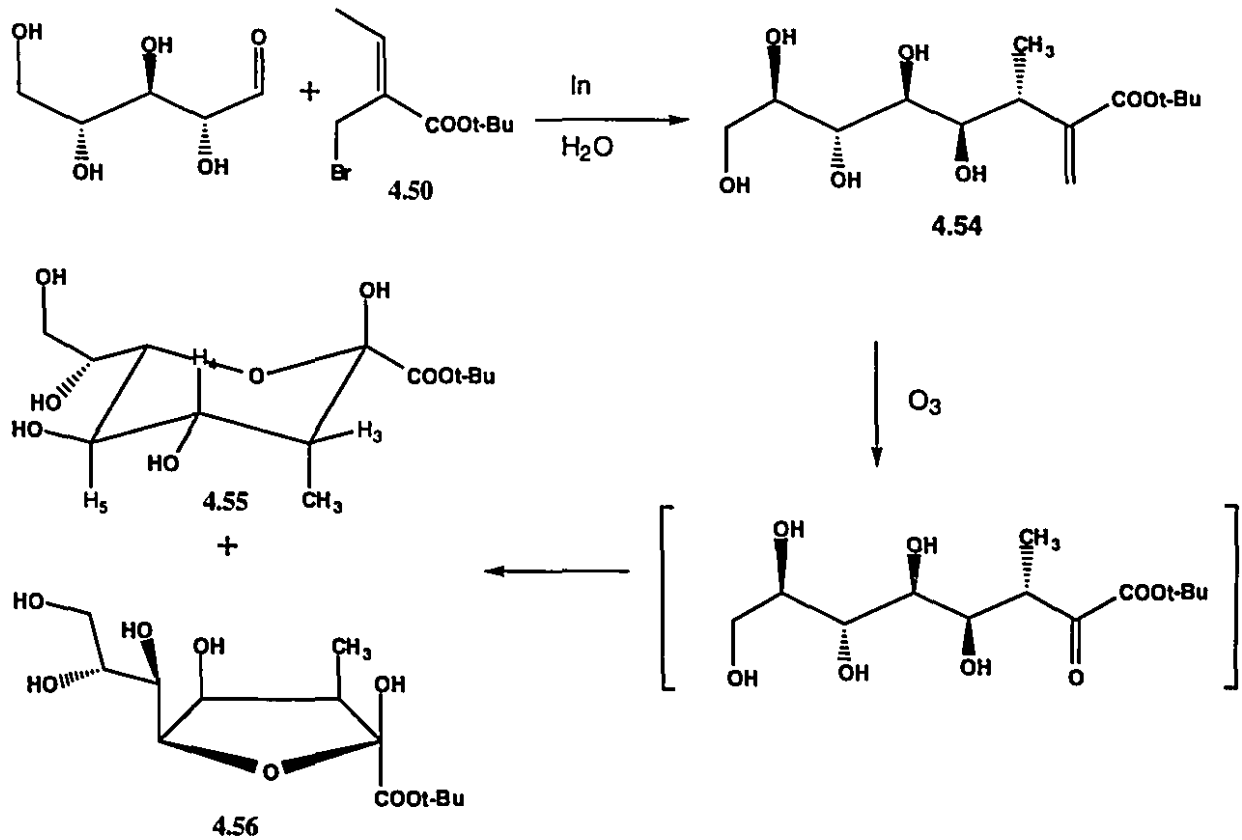
(4) **Stereoselective coupling of D-arabinose and D-ribose with t-butyl 2-bromomethyl-2-Z-butenoate (4.50)**. From the above results, it seems that in the indium mediated coupling of aldoses with γ-substituted allyl halides, the relative stereochemistry between Cα and Cβ is governed by the geometry of the allylindium species. If the geometry can be held to the cisoid structure, one might expect the anti- stereochemistry between Cα and Cβ. We tested this possibility by studying the coupling of t-butyl 2-bromomethyl-2-Z-butenoate (**4.50**).[26] Coupling of **4.50** with D-arabinose and indium in water gave the product as a mixture of two compounds in a ratio of 8:1 in 86% combined yield. The major isomer **4.51** was purified by flash chromatography. Subsequent ozonolysis of **4.51** gave the cyclic compound **4.52** as a pyranose. Treatment of **4.52** with trifluoroacetic acid in water gave an ene lactone which is assigned the structure **4.53**. Similar ene lactone structure has been obtained from the acid treatment of 3-deoxy-D-*manno*-2-octulosonic acid (KDO **4.2**).[27]



Scheme 4.15

The relative stereochemistry of Cα, Cβ and Cγ in **4.52** would be difficult to distinguish on the basis of nmr coupling constants since the two small coupling constants (J = 3.42 Hz and J = 4.39 Hz) are compatible with either syn-syn or syn-anti stereochemistry. In an attempt to resolve this enigma, D-ribose was coupled to **4.50** in the presence of indium and water to give the product as a mixture of two compounds in a ratio of approximately 10 : 1 in 82 % yield. The

major isomer **4.54** was purified by flash chromatography. Subsequent ozonolysis of **4.54** gave a mixture consisting primarily of two isomers **4.55** and **4.56**. On standing at room temperature for 7 days, the complex mixture mutarotated to give the more thermodynamically favorable anomer **4.55.** Using 2D-homonuclear spectroscopy (COSY) and coupling constant analysis, the relative syn, anti stereochemistry of **4.55** ($J_{H3,H4}$ = 5.37 Hz and $J_{H4,H5}$ = 9.77 Hz) and **4.56**, and thus **4.54** was confirmed.



Scheme 4.16

4.4 Conclusions

Results from this study suggest that in the indium mediated coupling of aldoses with γ-substituted allyl halides, the reaction can be stereoselective. The preferred relative stereochemistry of Cγ and Cβ is syn. This is explained by chelation of the α-hydroxy carbonyl function with indium, and that the allyl

indium species attacks from the less hindered face of the chelate. This conclusion is similar to the one drawn by Paquette on simple α-hydroxy and α-alkoxy aldehydes.[16] The relative stereochemistry of the Cα and Cβ centres appears to be controlled by the geometry of the substituted allyl indium species. With this information, it should be possible to design stereoselective synthesis of a number of 2-deoxy-2-substituted aldoses and 3-deoxy-3-substituted-2-keto-ulosonic acids.

Experimental

General.. Chemicals were purchased from Aldrich and were reagent grade. Hexanes, ethylacetate, dichloromethane, were distilled over calcium hydride Analytical thin layer chromatography was performed on silica gel 60 F_{254} plastic back 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 (10 ml / 90 ml) and heated with a heat gun.

The Nuclear Magnetic Resonance spectra were recorded on a VARIAN Gemini 200 (^1H 500 MHz, ^{13}C 50 MHz) or a Unity 500 MHz (^1H 200 MHz, ^{13}C 125 MHz) spectrometer and chemical shifts are reported on the δ scales in parts per million (ppm) with solvent residue as references. Singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) were recorded at the centre of the peaks and were used throughout. IR spectra were recorded on an Analet FT A25-18 spectrometer between NaCl plates. Mass spectra were recorded on a Kratos MS25RFA mass spectrometer. Melting points were determined on a Gallenkamp block and were uncorrected. Optical rotations were done on a JASCO DIP-140 polarimeter.

General procedure for the coupling of cinnamyl bromide with aldoses : To a solution of the carbohydrate (1 mmol) and cinnamyl bromide (2 mmol) in 15ml of H_2O, was added indium powder (150 mesh, 2 mmol). The reaction mixture was vigorously stirred at room temperature for 15 hrs. Water was then removed under reduced pressure and the product mixture was taken up into methanol and decanted into a round bottom flask. The methanolic solution was concentrated and then purified by flash chromatography (methanol: methylene chloride 1: 10).

General procedure for the synthesis of the 2-deoxy-2-phenylaldoses : Through a methanolic solution of the adduct obtained above at -78°, was bubbled O_3. The reaction mixture was purged with argon and Ph_3P (2 eq) was added. The mixture was allowed to come to room temperature and stirring was continued for 15 hrs. The solvent was removed under reduced pressure and the crude product mixture was purified by flash chromatography (methanol: methylene chloride).

(2RS,3RS)-2,3-Dihydroxy-4-phenyl-5-hexene-1-ol: Colourless oil; ^1H NMR (syn-syn isomer, **4.11**; major) (D_2O) δ 7.10 -7.30 (m, 5H), 5.87 (dt, 1H, J= 9.77 and 17.10 Hz), 5.05 (dd, 1H, J= 1.22 and 17.10 Hz), 4.97 (dd, 1H, J= 1.22 and 9.77 Hz), 3.87 (dd, 1H, J=1.95 and 10.25 Hz); 3.74 (ddd, 1H, J=1.95, 5.37 and 7.32 Hz), 3.52 (dd, 1H, J=5.37 and 11.72 Hz), 3.48 (dd, 1H, J=9.77 and 10.25 Hz), 3.42(dd, 1H, 7.32 and 11.72 Hz); ^{13}C NMR (CD_3OD) δ 55.19, 65.24, 71.97, 74.55, 116.77, 127.34, 129.41, 129.65, 140.65, 143.36; MS m/z 209 $(M + H)^+$; HRMS(FAB) calcd for $C_{12}H_{16}O_3$ $(M + H)^+$ 209.11777, found 209.11781.

^{1}H NMR (anti-syn isomer, **4.12**, minor) (D_2O) δ 7.10 -7.30 (m, 5H), 6.02 (ddd, 1H, J=9.28, 10.23 and 17.10 Hz), 5.04 (dd, 1H, J= 1.22 and 17.10 Hz), 5.02 (dd,1H, J= 1.22 and 10.23 Hz), 3.79 (dd, J=2.44 and 9.28 Hz) , 3.74 (ddd, 1H, J=2.44, 5.37 and 7.32 Hz), 3.55 (1H, J= 5.37 and 11.23 Hz), 3.45 (t,1H, J= 9.28 Hz), 3.42 (dd, 1H, 7.32 and 11.23 Hz); ^{13}C NMR (CD_3OD) δ 54.68, 65.19, 71.78, 75.12, 116.84, 127.55, 129.54, 129.63, 140.99, 143.09; MS m/z 209 $(M + H)^+$; HRMS(FAB) calcd for $C_{12}H_{16}O_3$ $(M + H)^+$ 209.11777, found 209.11781.

(2R,3R,4RS,5RS)-2,3,4-Trihydroxy-5-phenyl-6-heptene-1-ol (from D-erythrose) ^{1}H NMR (4R, 5R isomer, **4.25**; major) (D_2O) δ 7.10 -7.30 (m, 5H), 5.83 (dt,1H, J= 9.77 and 17.10 Hz), 5.05 (dd, 1H, J=1.47 and 17.10 Hz), 4.94 (dd, 1H, J=1.47 and 9.77 Hz), 4.08 (d, 1H, J=9.77 Hz), 3.69 (m, 1H), 3.58 (m, 2H), 3.49 (dd,1H, J=9.77 and 10.26), 3.45 (m, 1H); ^{13}C NMR (D_2O) δ 53.17, 63.11, 69.72, 70.95, 71.35, 116.68, 126.67, 127.94, 128.80, 138.57, 142.13; MS m/z 261 $(M + Na)^+$; HRMS(FAB) calcd for $C_{13}H_{18}O_4$ $(M + Na)^+$ 261.11028, found 261.11037.

^{1}H NMR (4S, 5S isomer, **4.26**, minor) (D_2O) δ 7.10 -7.30 (m, 5H), 6.03 (ddd,1H, J= 9.28, 10.26 and 17.10 Hz), 5.04 (dd, 1H, J=1.22 and 17.10 Hz), 5.00 (dd, 1H, J= 1.22 and 10.26), 4.02 (d, 1H, J=10.74 Hz), 3.69 (m,1H,) 3.58 (m, 2H), 3.49 (dd, 1H, J= 9.28 and 10.74), 3.45 (m, 1H); ^{13}C NMR (D_2O) δ 52.87, 62.99, 69.58, 70.95, 71.73, 116.69, 126.78, 127.95, 128.92, 139.72, 141.26; MS m/z 261 $(M + Na)^+$; HRMS(FAB) calcd for $C_{13}H_{18}O_4$ $(M + Na)^+$ 261.11028, found 261.11037.

(2R,3R,4R,5RS,6RS)-2,3,4,5-Tetrahydroxy-6-phenyl-7-octene-1-ol (from D-ribose) ^{1}H NMR (5R,6R isomer, **4.29**; major) (D_2O) δ 7.10 -7.30 (m, 5H), 5.83 (ddd,1H, J=9.77 Hz, 10.26 Hz, 17.33 Hz), 5.07 (dd, 1H, J= 1.95 and

17.33 Hz), 4.95 (dd,1H, J= 1.95 and 10.26 Hz), 4.07 (d, 1H, J=10.74 Hz), 3.80 (ddd, 1H, J=2.93, 4.40 and 7.81 Hz), 3.69 (t, 1H, J= 9.28 Hz), 3.67 (dd, 1H, J=4.40 and 9.28 Hz), 3.64 (dd,1H, J= 2.93 and 11.72 Hz), 3.52 (dd,1H, J= 7.81 and 11.72 Hz), 3.49 (dd, 1H, J= 9.77 and 10.74 Hz); ^{13}C NMR (D_2O) δ 53.06, 61.63, 69.86, 71.57, 71.60, 72.50, 116.72, 126.65, 127.87, 128.77, 138.41, 142.01; MS m/z 269 $(M + H)^+$; HRMS(FAB) calcd for $C_{14}H_{20}O_5$ $(M + H)^+$ 261.13890, found 261.13893.

^1H NMR (5S,6S isomer **4.30**, minor) δ 7.10 -7.30 (m, 5H), 6.04 (ddd, 1H, J=9.28, 10.25 and 17.10 Hz), 5.04 (dd, 1H, J= 1.22 and 17.10 Hz), 4.99 (dd, 1H, J= 1.22, 10.25 Hz), 4.04 (dd, 1H, J=0.98 Hz, 10.25 Hz), 3.64 (ddd, 1H, J= 2.93, 7.33, 7.81 Hz), 3.59 (dd, 1H, J= 4.88 and 7.81 Hz), 3.45 (dd, 1H, J= 9.28 Hz and 10.25 Hz), 3.40 (dd, 1H, J= 2.93 and 11.72 Hz), 3.31 (dd, 1H, J= 7.33 and 11.72 Hz), 3.04 (dd, 1H, J= 0.98 and 7.81 Hz); ^{13}C NMR (D_2O) δ 52.83, 61.63, 69.70, 71.49, 71.60, 71.94, 116.66, 126.65, 127.87, 128.77, 138.41, 142.01; MS m/z 269 $(M + H)^+$; HRMS(FAB) calcd for $C_{14}H_{20}O_5$ $(M + H)^+$ 261.13890, found 261.13893.

(2R,3R,4S,5RS,6RS)-2,3,4,5-Tetrahydroxy-6-phenyl-7-octene-1-ol (from D-arabinose) ^1H NMR (5S, 6S isomer, **4.33;** major) (D_2O) δ 7.10 -7.30 (m, 5H), 5.90 (ddd,1H, J= 9.28, 10.25 and 17.10 Hz), 5.05 (dd, 1H, J= 1.47 and 17.10 Hz), 4.97 (dd, 1H, J= 1.47 and 10.25 Hz), 3.98 (dd, 1H, J= 2.44 and 9.28 Hz), 3.79 (dd, 1H, J= 2.44 and 2.93 Hz), 3.61 (dd, 1H, J= 2.93 and 7.81 Hz), 3.60 (dd, 1H, J=2.93 and 7.32 Hz), 3.49 (t, 1H, J= 9.28 Hz), 3.45 (m, 2H); ^{13}C NMR (D_2O) δ 53.16, 62.37, 68.54, 71.02, 73.21, 75.10, 116.79, 126.75, 128.18, 128.76, 138.56, 141.34; MS m/z 291 $(M + Na)^+$; HRMS(FAB) calcd for $C_{14}H_{20}O_5$ $(M + Na)^+$ 291.12084, found 291.12098.

^{1}H NMR (5R, 6R isomer **4.34**, minor) (D_2O) δ 7.10 -7.30 (m, 5H), 6.02 (ddd, 1H, J= 9.28 Hz, 10.25 Hz, 17.10 Hz), 5.03 (dd, 1H, J=1.47 and 17.10Hz), 4.97 (dd, 1H, J= 1.47 and 10.25 Hz), 3.87 (dd, 1H, J= 3.42 and 8. 30 Hz), 3.58-3.60 (m, 2H), 3.49-3.52 (m, 2H) 3.46 (m, 2H); ^{13}C NMR (D_2O) δ 52.62, 62.23, 68.93, 70.90, 72.51, 74.97, 117.40, 126.80, 127.93, 128.84, 138.06, 141.44; MS m/z 291 $(M + Na)^+$; HRMS(FAB) calcd for $C_{14}H_{20}O_5$ $(M + Na)^+$ 291.12084, found 291.12098.

2-Deoxy-2-phenyl-ribopyranose A quantity of 40 mg (0.2 mmols) of the glyceraldehyde coupled adducts **4.11** and **4.12** was ozonised. 30 mg (75% yield) of pyranose (**4.13** and **4.14**) was isolated as a colourless gum. ^{1}H NMR (β anomers **4.13a**) (D_2O) δ 7.10 -7.40 (m, 5H), 4.82 (d, 1H, J= 9.28 Hz), 3.87 (dd, 1H, J=5.37 and 11.23 Hz), 3.67 (dd, 1H, J= 9.28 and 10.74 Hz), 3.54 (ddd, 1H, J= 5.37, 9.28 and 10.74 Hz), 3.33 (t,1H, J= 11.23 Hz), 2.48 (dd,1H, J= 9.28 and 11.23 Hz); ^{13}C NMR (D_2O+ DMSO-d_6) δ 56.78, 65.99, 71.27, 75.49, 98.33, 126.55, 128.33, 129.34; 140.10;

^{1}H NMR (α anomers **4.13b**) (D_2O + DMSO-d_6) δ 7.10 -7.40 (m, 5H), 4.88 (d, 1H, J= 2.93 Hz), 3.91 (dd, 1H, J=5.37 and 11.72 Hz), 3.60 (dd, 1H, J= 9.28 and 10.74 Hz), 3.37 (ddd, 1H, J= 5.37, 9.28 and 11.23 Hz), 3.20 (dd, 1H, J= 11.23 and 11.72 Hz), 2.71 (dd,1H, J= 2.93 and 10.74 Hz); ^{13}C NMR (D_2O+ DMSO-d_6) δ 53.97, 62.11, 70.60, 72.20, 94.46, 127.97, 128.08, 130.07; 139.19;

^{1}H NMR (β anomers **4.14a**) (D_2O + DMSO-d_6) δ 7.10 -7.40 (m, 5H), 4.88 (d,1H, J= 2.93 Hz), 4.16 (dd, 1H, J=5.37 Hz, 11.72 Hz), 3.82 (dd, 1H, J= 9.28 Hz, 10.74 Hz), 3.68 (m, 1H, J= 5.37 Hz, 9.28 Hz, 10.74 Hz), 3.38 (dd,1H, J= 11.23 Hz), 2.93 (dd,1H, J= 9.28 Hz, 11.23 Hz); ^{13}C NMR (D_2O+ DMSO-d_6) δ 49.30, 65.31, 68.23, 72.40, 93.93, 126.22, 128.26, 129.93; 140.97; MS FAB : (unstable)

2-Deoxy-2-phenyl-glucopyranose A quantity of 72 mg (0.3 mmol) of the erythrose coupled adducts (predominantly **4.25** after purification) was ozonized. 71 mg (98%) of the product **4.27** was obtained as an anomeric mixture. ^{1}H NMR D_2O) (β anomer of **4.27**) δ 7.20-7.40 (m, 5H), 4.90 (d, 1H, J= 8.79 Hz), 3.79 (dd, 1H, J= 1.95 and 12.15 Hz), 3.74 (dd, 1H, J= 9.28 and 10. 74 Hz), 3.64 (dd, 1H, J= 5.86 and 12.15 Hz), 3.48 (ddd, 1H, J= 1.95, 5.86 and 9.77 Hz), 3.33 (dd,1H, J= 9.28 and 9.77 Hz), 2.51 (dd, 1H, J= 8.79 and 10.74 Hz); ^{13}C NMR (D_2O) d= 56.06, 60.67, 70.28, 74.98, 75.75, 96.57, 127.41, 128.34, 128.74, 136.71; MS m/z 263 $(M + Na)^+$; HRMS(FAB) calcd for $C_{12}H_{16}O_5$ $(M + Na)^+$ 263.08954, found 263.08956.

2-Deoxy-2-phenyl-gluco-hepto-pyranose A quantity of 111 mg (0.4 mmol) of the ribose coupled adduct **4.29/4.30** was ozonised. Chromatographic isolation yielded 96.5 mg (87%) of an aldose mixture which was predominantly the β anomer of **4.31**. ^{1}H NMR (D_2O) (β anomer **4.31**) δ 7.10-7.35 (m, 5H), 4.86 (d,1H, J= 8.79 Hz), 3.93 (dt, 1H, J= 3.42 and 7.33 Hz), 3.71 (dd, 1H, J= 8.79 and 10.74 Hz), 3.69 (dd, 1H, J= 7.33 and 11.72 Hz), 3.54 (dd, 1H, J= 3.42 and 9.77 Hz), 3.43 (dd, 1H, J= 8.79 and 9.77 Hz), 2.50 (dd, 1H, J= 8.79 and 10.74 Hz); ^{13}C NMR (D_2O) δ 55.91, 61.48, 71.06, 71.60, 75.19, 76.02, 96.80, 127.43, 128.35, 128.74, 136.64; MS m/z 293 $(M + Na)^+$; HRMS(FAB) calcd for $C_{13}H_{18}O_6$ $(M + Na)^+$ 293.10011, found 293.10011.

Procedure for coupling of cinnamyl bromide to (R)-2-O-benzyl glyceraldehyde 4.20: To a rapidly stirred solution of **4.20** (140mg, 0.85 mmol) and cinnamyl bromide (0.335mg, 2eq) in 5ml of H_2O , was slowly added indium powder (150 mesh, 2 mmol). The reaction mixture was vigorously stirred

at room temperature for 15 hrs. The mixture was extracted with ethyl acetate (2 x 15 ml). The organic layer was separated, dried with $MgSO_4$, filtered and the solvent was then removed under reduced pressure. The crude mixture was purified by flash chromatography (hexane: ethylacetate = 1: 4). The product **4.21** (a mixture of isomers **4.21a** and **4.21b**) was obtained as a light yellow oil (209mg, 82.5%);

(2R,3R,4R)-2-Benzyloxy-3-hydroxy-4-phenyl-5-hexene-1-ol **(4.21a)** ^1H NMR ($CDCl_3$) (major isomer) δ 7.15-7.45 (m, 10H), 5.98 (ddd, 1H, J=9.28, 10.25 and 17.10 Hz), 5.09 (dd, 1H, J= 1.47 and 10.25), 5.05 (dd, 1H, J= 1.47 and 17.10 Hz), 4.73 (d, 1H, J= 11.72 Hz), 4.56 (d, 1H, J= 11.72 Hz), 4.04 (dd, 1H, J= 2.93 and 8.80 Hz), 3.93 (dd, 1H, J= 4.88 and 11.72 Hz), 3.79 (dd, 1H, J=3.91 and 11.72 Hz), 3.64 (ddd, 1H, J=2.93, 3.91 and 4.88 Hz), 3.62 (dd, 1H, J= 8.80 and 9.28 Hz). ^{13}C NMR ($CDCl_3$) δ 53.72, 62.40, 72.30, 75.13, 77.63, 116.96, 126.70, 127.82, 127.88, 128.29, 128.37,128.58, 137.88, 138.34, 140.58; MS m/z 299 $(M + H)^+$; HRMS(FAB) calcd for $C_{19}H_{22}O_3$ $(M + H)^+$ 299.16472, found 299.16470.

(2R,3S,4S)-2-Benzyloxy-3-hydroxy-4-phenyl-5-hexene-1-ol **(4.21b)** ^1H NMR ($CDCl_3$) (minor isomer) δ 7.15-7.45 (m, 10H), 6.18 (ddd, 1H, J= 8.79, 10.25 and 17.10 Hz), 5.22 (dd, 1H J= 1.47 and 10.25 Hz), 5.19 (dd, 1H, J= 1.47 and 17.10 Hz), 4.61 (d, 1H, J= 11.23 Hz), 4.45 (d, 1H, 11.23 Hz), 4.00 (dd, 1H, J= 2.93 and 8.79 Hz), 3.86 (dd, 1H, J= 3.91 and 11,72), 3.70 (dd, 1H, J= 4.40 and 11.72 Hz), 3.59 (t, 1H, J= 8.79 Hz), 3.20 (ddd, 1H, J= 2.93, 3.91 and 4.40 Hz); ^{13}C NMR ($CDCl_3$) δ 53.45, 62.31, 72.11, 75.38, 77.26, 118., 126.65, 127.76, 127.79, 128.46, 128.64, 128.69, 137.32, 138.55, 140.90; MS m/z 299 $(M + H)^+$; HRMS(FAB) calcd for $C_{19}H_{22}O_3$ $(M + H)^+$ 299.16472, found 299.16470.

Synthesis of 4.22 To a solution of **4.21** (100mg, 0.33 mmol) in dimethoxypropane (DMP) was added catalytic amount of TsOH. The reaction mixture was stirred at room temperature for 12h. Removal of the solvent under reduced pressure gave quantitatively the product **4.22** as a white solid which was recrystallised from isopropyl ether (IPE); mp 105-108°. ^{1}H NMR ($CDCl_3$) d 7.18-7.50 (m, 10H), 5.81 (ddd, 1H, J=8.79, 10.01 and 17.09 Hz), 5.07 (dd, 1H, J= 1.71 and 17.09 Hz), 5.04 (dd, 1H, J= 1.71 and 10.01 Hz), 4.72 (d, 1H, J= 11.72 Hz), 4.52 (d, 1H, J= 11.72 Hz), 4.17 (dd, 1H, J= 1.71 and 10.25 Hz), 4.05 (dd, 1H, J= 2.20 and 12.94 Hz), 3.91 (m, 2H), 3.41 (dd, 1H, J= 1.71 and 2.20 Hz), 1.30 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 18.52, 28.63, 50.33, 61.53, 70.37, 70.98, 73.06, 98.68, 117.13, 125.93, 127.46, 127.91, 127.97, 128.03, 128.06, 128.13, 137.44, 138.11,141.27; MS m/z 339 $(M + H)^+$; HRMS(FAB) calcd for $C_{22}H_{26}O_3$ $(M + H)^+$ 339.19602, found 339.19599.

Synthesis of 4.23. Through a solution of **4.21** (60 mg, 0.2 mmol) in CH_2Cl_2 at -78 was bubbled O_3 for 30 min. Triphenylphosphine(105 mg, 2eq) was added and the mixture allowed to warm to room temperature and stirred overnight.. Removal of solvent followed by flash column chromatography gave **4.23** as a white solid (84%) which was recrystallised from $CHCl_3$; mp: 159-160° $[\alpha]^{25}_D$= + 60° (c=0.102, $CHCl_3$) ^{1}H NMR (α anomer of **4.23**) ($CDCl_3$) δ 7.30 (m,10H), 5.17 (d, 1H, J= 3.42 Hz), 4.73 (s, 2H), 4.44 (dd, 1H, J= 8.79 and 9.28 Hz) 3.82 (dd, 1H, J= 5.37 and 11.72 Hz), 3.62 (ddd, 1H, J= 5.37, 8.79 and 10.25 Hz), 3.42 (10.25 and 11.72 Hz), 2.94 (dd, 1H, J=3.42 and 9.28 Hz); ^{13}C ($CDCl_3$) 53.79, 60.37, 70.36, 73.00, 79.38, 94.59, 126-129 (overlapping), 135.63, 137.48; MS m/z 301 $(M + H)^+$; HRMS(FAB) calcd for $C_{18}H_{20}O_4$ $(M + H)^+$ 301.14398, found 301.14410.

^{1}H NMR ($CDCl_3$) (β anomer of **4.23**) δ 7.30 (m,10H), 4.84 (d, 1H, J= 8.30 Hz), 4.71 (s, 2H), 4.13 (dd,1H, J= 5.37 and 11.23 Hz), 3.96 (dd, 1H, J=8.30 and 10.74 Hz), 3.95 (dd, 1H, J= 10.74 and 11.23 Hz), 3.62 (ddd, 1H, J= 5.37, 8.30 and 11.23 Hz), 2.70 (dd, 1H, J=8.30 and 10.74 Hz) ^{13}C ($CDCl_3$) 56.50, 64.22, 73.06, 74.81, 78.24, 97.83, 126-141 (overlapping); MS m/z 301 $(M + H)^+$; HRMS(FAB) calcd for $C_{18}H_{20}O_4$ $(M + H)^+$ 301.14398, found 301.14410.

Procedure for coupling of methyl 4-bromo-E-crotonate (4.6c) to aldoses : To a solution of the carbohydrate (1 mmol) and methyl 4-bromo-E-crotonate (450 mg, 2.5 mmol) in 5ml of H_2O , was added indium powder (345 mg, 3 mmol). The reaction mixture was vigorously stirred at room temperature for 15 hrs. The water was then removed under reduced pressure and product mixture was taken up into methanol and decanted into a round bottom flask. The product mixture was concentrated and then purified by flash chromatography (methanol: methylene chloride = 1: 19).

Procedure for the synthesis of the 2-deoxy-2-methoxycarbonyl aldoses : Through a methanolic solution of the homoallylic carbohydrate at -78° was bubbled O_3. The reaction mixture was purged with argon and Me_2S (2 eq) was added. The mixture was allowed to come to room temperature and stirring was continued for 15 hrs. The solvent was removed under reduced pressure and the crude product mixture purified by flash chromatography (MeOH : CH_2Cl_2 = 1: 10).

2,3-Dihydroxy-4-methoxycarbonyl-5-hexene-1-ol (4.48): ^{1}H NMR (D_2O) δ 5.78 (dt, 1H, J= 9.77 and 18.07 Hz), 5.28 (dd, 1H, J= 1.20 and 18.07

Hz), 5.23 (dd, 1H, J= 1.20 and 9.77 Hz), 3.89 (dd, 1H, J= 0.97 and 9.77 Hz); 3.63 (s, 3H), 3.60 (m, 2H), 3.58 (dd, 1H J=2.24 and 7.32 Hz), 3.33 (1H, J=3.42 and 7.32 Hz); ^{13}C NMR (D_2O) d= 56.24, 57.63, 66.33, 73.51, 74.45, 123.45, 134.23, 177.57; MS m/z 191 $(M + H)^+$; HRMS(FAB) calcd for $C_8H_{14}O_5$ $(M + H)^+$ 191.09195, found 191.09187.

2-Deoxy-2-methoxycarbonyl-ribopyranose (4.49) : A quantity of 20 mg (0.1 mmols) of the glyceraldehyde coupled adduct **4.48** was ozonised. 16.7 mg (83% yield) of a colourless viscous liquid was isolated as an anomeric mixture; ^1H NMR (D_2O) (for the β anomer of **4.49**, major) δ 4.76 (d, 1H, J= 8.79 Hz), 3.81 (dd, 1H, J=5.37 and 11.23 Hz), 3.64 (dd, 1H, J=10.74 and 11.23 Hz), 3.63 (s, 3H), 3.45 (ddd, 1H, J= 5.37, 10.74 and 11.23 Hz), 3.19 (dd, 1H, J= 10.74 and 11.23 Hz), 2.42 (dd, 1H, J= 8.79 and 11.23 Hz); ^{13}C NMR (D_2O) δ 56.52, 60.07, 68.82, 72.73, , 75.91, 98.05, 174.87; MS m/z 193 $(M + H)^+$; HRMS(FAB) calcd for $C_7H_{12}O_6$ $(M + H)^+$ 193.07121, found 193.07117.

^1H NMR (D_2O) (for the α anomer of **4.49**, minor) δ 5.31 (d,1H, J= 3.90 Hz), 3.93 (dd, 1H, J=8.79 and 10.74 Hz), 3.65 (dd, 1H, J=5.37 and 11.23 Hz), 3.62 (s, 3H), 3.45 (ddd, 1H, J= 5.37, 8.79 and 11.23 Hz), 3.19 (dd, 1H, J= 10.74 and 11.23 Hz), 2.71 (dd,1H, J= 3.90 and 10.74 Hz); ^{13}C NMR (D_2O) δ 56.36, 64.51, 70.03, 72.04, , 73.16, 94.41; 173.00; MS m/z 193 $(M + H)^+$; HRMS(FAB) calcd for $C_7H_{12}O_6$ $(M + H)^+$ 193.07121, found 193.07117.

Procedure for the coupling of crotyl bromide to aldoses : To a solution of the carbohydrate (1 mmol) and crotyl bromide (338 mg, 2.5 mmol) in 5ml of H_2O, was added indium powder (345 mg, 3 mmol). The reaction mixture was vigorously stirred at room temperature for 15 hrs. The water was then

removed under reduced pressure and the product mixture was taken up into methanol and decanted into a round bottom flask. The product mixture was concentrated and then purified by flash chromatography (methanol: methylene chloride = 1: 10).

2,3-Dihydroxy-4-methyl-5-hexene-1-ol: ^{1}H NMR (mixture of 4 isomers) (D_2O) δ 5.55-5.80 (1H), 4.80-5.00 (2H), 3.35-3.70, (4H), 2.20-2.5 (1H), 0.75-0.95 (3H); ^{13}C NMR (D_2O) δ 10.96, 13.48, 16.41, 37.82, 38.21, 39.20, 39.36, 62.50, 62.98, 63.04, 68.81, 69.09, 69.16, 69.23, 69.37, 69.78, 70.75, 70.79, 70.84, 71.09, 71.84, 72.75, 73.25, 75.53, 75.59, 114.22, 114.83, 115.78, 116.19, 138.46, 139.21, 141.04, 142.01; MS m/z 169 $(M + Na)^+$; HRMS(FAB) calcd for $C_7H_{14}O_3$ $(M + Na)^+$ 169.08406, found 169.08399.

2,3,4,5-Tetrahydroxy-6-methyl-7-octene-1-ol (from D-ribose)

^{1}H NMR (mixture of 4 isomers) (D_2O) δ 5.50-5.70 (1H), 4.80-5.00 (2H), 3.20-3.70 (6H), 2.20-2.40 (1H), 0.75-0.95 (3H); ^{13}C NMR (D_2O) δ 12.82, 14.81, 16.19, 16.23, 38.56, 38.62, 39.71, 39.75, 62.23, 62.61, 62.75, 62.96, 71.37, 71.60, 71.83, 73.96, 74.20, 74.55, 74.77, 114.53, 114.88, 115.43, 115.88, 138.99, 140.20, 140.93, 141.28; MS m/z 207 $(M + H)^+$; HRMS(FAB) calcd for $C_9H_{18}O_5$ $(M + H)^+$ 207.12325, found 207.12318.

Synthesis of t-butyl 4,5,6,7,8-pentahydroxy-3-methyl-2-methylene-octanoate **(4.51)** : To a stirred solution of D-arabinose (150 mg,1 mmol) in H_2O (10 ml) was added **4.50** (705 mg, 3 mmol). To this mixture was added indium powder (345 mg, 3 mmol). The reaction mixture was stirred catalytic amount of Ts-OH. The reaction mixture was stirred at room temperature for 15 hrs. The water was evaporated. The residue was diluted with methanol and

filtered through celite. The methanol was removed in vacuo and and the residue purified by flash chromatography (CH_3OH : CH_2Cl_2 = 1 : 20). Isolated yield of **4.51**: 264 mg (86%) ^1H NMR (CD_3OD) δ 6.05 (s, 1H), 5.58 (s, 1H), 3.76 (dd, 1H, J= 2.44 and 5.37 Hz), 3.70 (dd, 1H, J= 2.44 and 7.81 Hz), 3.65 (dd, 1H, J= 3.42 and 11.23 Hz), 3.58 (m,1H) 3.53 (dd, 1H,J= 2.44 and 5.37 Hz), 3.50 (dd 1H, J=5.86 and 11.23 Hz), 2.90 (dq, 1H, J= 6.84 and 7.81 Hz) 1.38 (s, 9H); 1.02 (d, 3H, J= 6.84 Hz) ^{13}C NMR (CD_3OD) 17.85, 28.60, 39.65, 64.36, 69.45, 72.63, 75.47, 78.05, 81.76, 124.74, 144.78, 167.39; MS m/z 307 $(M + H)^+$; HRMS(FAB) calcd for $C_{14}H_{26}O_3$ $(M + H)^+$ 307.17568, found 307.17572.

Synthesis of 4.52 : Through a methanolic solution of **4.51** (250 mg, 0.8 mmol) at -78° was bubbled O_3. The reaction mixture was purged with argon and Me_2S (2 eq) was added. The mixture was allowed to come to room temperature and stirring was continued for 15 hrs. The solvent was removed under reduced pressure and the crude product mixture purified by flash chromatography (MeOH : CH_2Cl_2 = 1: 10). 230 mg (93%) of product **4.52** was isolated as an anomeric mixture. (**Major anomer**) ^1H NMR (D_2O) δ 3.89 (dd, 1H, J= 1.47 and 2.44 Hz), 3.77 (dd, 1H, J= 1.46 and 3.91 Hz), 3.72 (ddd, 1H, J= 2.44, 5.36 and 11.72 Hz), 3.70 (dd,1H, J=2.93 and 3.91 Hz) 3.62 (dd, 1H, J= 2.44 and 11.72 Hz), 3.45 (dd, 1H, J=5.86 and 11.72 Hz), 2.30 (qd, 1H, J= 2.93 and 7.32 Hz) 1.45 (s, 9H); 0.81 (d, 3H, J= 7.32 Hz) ^{13}C NMR (D_2O) δ 10.61, 26.67, 32.09, 62.58, 66.24, 66.39, 68.62, 71.18, 84.92, 98.24, 169.51; MS m/z 309 $(M + H)^+$; HRMS(FAB) calcd for $C_{13}H_{24}O_8$ $(M + H)^+$ 309.15494, found 309.15480.

(**Minor anomer**) ^1H NMR (D_2O) δ 4.17 (dd, 1H, J= 3.42 and 4.39 Hz), 4.05 (dd, 1H, J= 3.42 and 5.86 Hz), 3.83 (dd, 1H, J= 5.86 and 6.35 Hz), 3.64 (ddd, 1H, 2.44, 5.86 and 11.72 Hz), 3.50 (dd, 1H, J= 2.44 and 7.23 Hz), 3.48 (dd, 1H,

J=5.86 and 11.23 Hz), 2.11 (dq, 1H, J= 4.39 and 6.84 Hz) 1.45 (s, 9H); 0.91 (d, 3H, J= 6.84 Hz) ^{13}C NMR (D2O) δ 6.80, 26.80, 45.45, 61.91, 71.15, 71.30, 73.71, 82.72, 84.55, 102.51, 170.69; MS m/z 309 $(M + H)^+$; HRMS(FAB) calcd for $C_{13}H_{24}O_8$ $(M + H)^+$ 309.15494, found 309.15480.

Synthesis of 4.53 A solution of **4.52** (100 mg, 0.32 mmol) in 10 ml of 20% trifluoroacetic acid was stirred at room temperature for 3 hrs. The reaction mixture was concentrated in vacuo. Aqueous ammonia was added to give a thick orange gum. Attempted recrystallisation from aqueous ethanol failed. The ethanol solvent was removed and the residue redissolved in distilled water. To this mixture was added ion exchange resin (Dowex 150). The resin was removed by filtration and the water removed under reduced pressure. The crude mixture was purified by flash chromatography($CH_3OH : CH_2Cl_2 = 1 : 20$) giving 68 mg (78%) of product . ^1H NMR (D_2O) (major isomer **4.53**) δ 1.80 (s, 3H), 3.40-3.80 (m, 6 H); ^{13}C NMR (D2O) (major isomer) 8.75, 62.33, 67.79, 71.01, 71.92, 82.77, 133.39, 137.26, 171.80; MS FAB: = unstable

Synthesis of 4.54 : To a stirred solution of D-ribose (150 mg,1 mmol) in H_2O (10 ml) was added **4.50** (705 mg, 3 mmol). To this mixture was added indium powder (345 mg, 3 mmol). The reaction mixture was stirred catalytic amount of Ts-OH. The reaction mixture was stirred at room temperature for 15 hrs. The water was evaporated. The residue was diluted with methanol and filtered through celite. The methanol was removed in vacuo and and the residue purified by flash chromatography ($CH_3OH : CH_2Cl_2 = 1 : 20$). Isolated yield of **4.54**: 250 mg (82%) ^1H NMR (CD_3OD) δ 6.15 (s, 1H), 5.58 (s, 1H), 3.95 (d, 1H, J= 9.78 Hz), 3.83 (ddd, 1H, J= 3.42, 5.37 and 5.86 Hz), 3.82 (dd, 1H, J= 5.37 and 11.23 Hz), 3.81 (d, 1H, J= 5.86 Hz), 3.78 (dd, 1H,J= 1.46 and 3.42 Hz), 3.72

(dd 1H, J=5.86 and 11.23 Hz), 2.99(dq, 1H, J= 6.84 and 9.28 Hz) 1.50 (s, 9H); 1.10 (d, 3H, J= 6.84 Hz) ^{13}C NMR (CD_3OD) δ 17.68, 28.60, 39.59, 64.29, 72.07, 73.42, 73.84, 74.25, 81.58, 123.92, 145.56, 167.42; MS m/z 307 $(M + H)^+$; HRMS(FAB) calcd for $C_{14}H_{26}O_3$ $(M + H)^+$ 307.17568, found 307.17575.

Synthesis of 4.55 : Through a methanolic solution of **4.54** (60 mg, 0.2 mmol) at -78° was bubbled O_3. The reaction mixture was purged with argon and Me_2S (2 eq) was added. The mixture was allowed to come to room temperature and stirring was continued for 15 hrs. The solvent was removed under reduced pressure and the crude product mixture purified by flash chromatography (MeOH : CH_2Cl_2 = 1: 10). 51 mg (85%) of product was isolated as an isomeric mixture. (**Major isomer, 4.55**) ^1H NMR (CD_3OD) δ 4.04 (dd, 1H, J= 5.37 and 9.77 Hz), 3.90 (dd, 1H, J= 4.88 and 8.79 Hz), 3.74 (dd, 1H, J= 3.42, and 9.77 Hz), 3.73 (m,2H), 3.62 (t, 1H, J= 9.77 Hz), 2.29 (qd, 1H, J= 5.37 and 7.33 Hz) 1.50 (s, 9H); 0.86 (d, 3H, J= 7.33 Hz) ^{13}C NMR (CD_3OD) δ 9.00, 28.10, 42.17, 64.18, 68.67, 71.73, 74.40, 75.93, 83.64, 98.66, 171.17; MS m/z 309 $(M + H)^+$; HRMS(FAB) calcd for $C_{13}H_{24}O_8$ $(M + H)^+$ 309.15494, found 309.15480.

(**Minor isomer, 4.56**) ^1H NMR (CD_3OD) δ 4.24 (t, 1H, J= 4.40 Hz), 4.04 (dd, 1H, J= 4.40 and 7.81 Hz), 3.99 (dd, 1H, J= 4.88 and 7.81 Hz), 3.83 (ddd, 1H, 3.90, 4.88 and 8.30 Hz), 3.76 (dd, 1H, J= 3.90 and 11.23 Hz), 3.68 (dd, 1H, J=8.30 and 11.23 Hz), 2.52 (dq, 1H, J= 4.40 and 6.84 Hz) 1.48 (s, 9H); 1.08 (d, 3H, J= 6.84 Hz) ^{13}C NMR (CD_3OD) δ 8.27, 28.08, 46.28, 64.13, 72.16, 74.53, 75.14, 75.93, 84.31, 104.50, 171.12.69; MS m/z 309 $(M + H)^+$; HRMS(FAB) calcd for $C_{13}H_{24}O_8$ $(M + H)^+$ 309.15494, found 309.15480.

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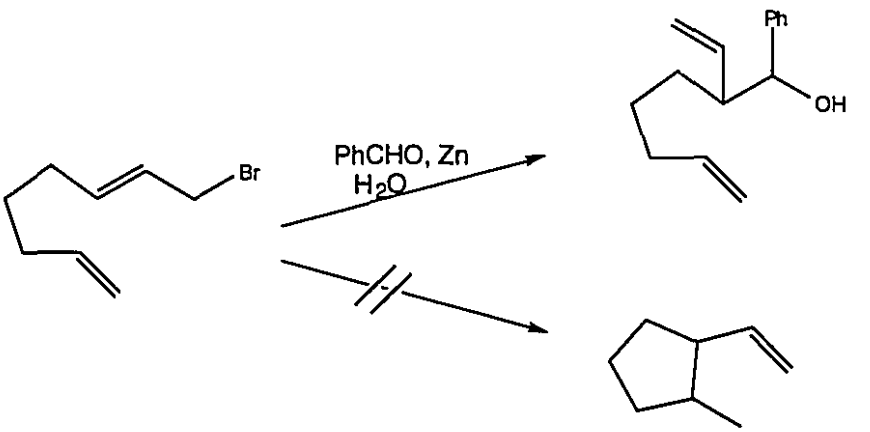
Chapter 5

Mechanistic Considerations and Future Development for the Aqueous Indium-Mediated Methodology

In the area of organometallic chemistry, many Barbier-type reactions have been conducted in water. These reactions basically concern the allylation of carbonyl compounds. Needless to say, this type of reaction was originally thought to be impossible in water because the postulated organometallic intermediate should be highly reactive with water. This meant that most of these types of reaction were performed by carefully excluding water. In fact, the allylation of carbonyl compounds using allyl halides and metals is now possible in water with good yields. The most interesting result to date concerns the use of indium metal which has been used to prepare octosulonic (KDO) and nonulosonic (KDN) acids. We have further studied and developed the indium-Barbier-type reactions (allylations and propargylation) to obtain heightened levels of regio- and diastereoselection. The diastereoselectivities that have been observed for the allylation of simple aliphatic and aromatic aldehydes seem to strongly suggest that chelate control can continue to operate in water. These findings were further corroborated by the fact that α-hydroxy aldehydes such as aldoses were coupled to simple allyl halides and γ-functionalised allyl halides with excellent diastereofacial control.

Despite the success of the aqueous indium-Barbier reaction, the precise mechanism still remains unclear. In the mid-1980's, Luche *et al.* [1] proposed the involvement of radical pairs for these aqueous metal-mediated reactions, and has suggested that a radical derived from the halide attack the carbonyl compound. Wilson *et al.* [2] subsequently investigated such a mechanism by the

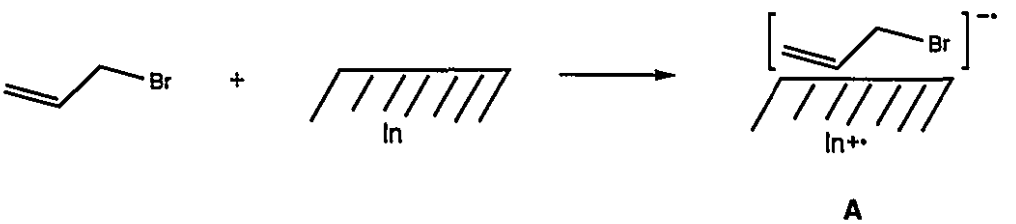
use of a radical probe and demonstrated unambiguously that radicals could not be involved (Scheme 5.1).



Scheme 5.1

Furthermore, the proposed free radical mechanism also contradicts the chemoselectivity associated with the allylation of α,β-unsaturated carbonyl compounds, in which exclusive 1,2 addition products were obtained, whereas radicals tend to undergo conjugate addition.

We have come to favor a single electron transfer (SET) process in which the allyl halide approaches the surface of the indium metal where the SET process generates the reactive radical anion/ indium cation pair **A** (Scheme 5.2).

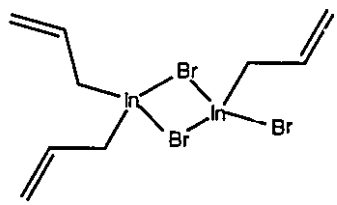


A

Scheme 5.2

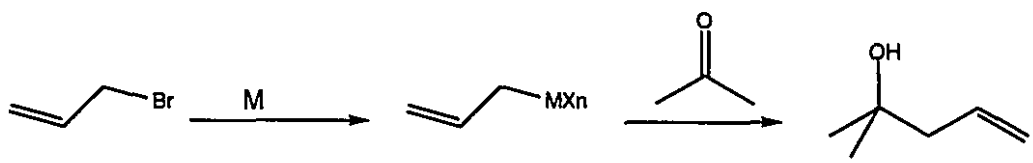
However, these conditions operate only when indium metal is present as a

reactant. Nevertheless, the preformation of allylindium reagents may well bypass the involvement of **A**, suggesting an alternative pathway involving the more conventional species **B**.[3]



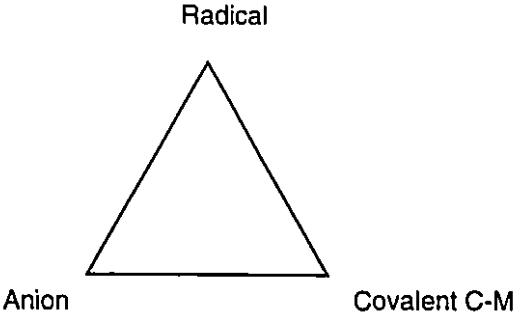
B

Work by Whitesides *et al.*, Grieco *et al* and Marshall *et al.* have shown that it is possible to carry out allylations in water with preformed allylmetal reagents. Such a result supports the proposed mechanism involving a discrete organometallic intermediate such as **B** (Scheme 5.3).[4,5,3]



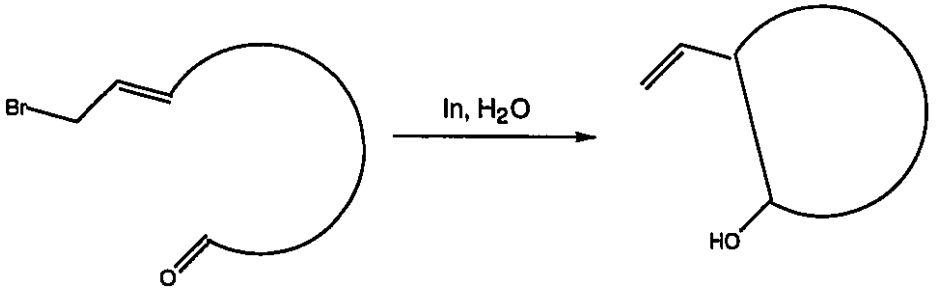
Scheme 5.3

In essence, an element of validity can be found in each of the proposed mechanism (radical, radical anion and preformed allyl metal reagent). Probably, one mechanism might reflect the actual details more than the others, depending on the metal, the substrate and the reaction conditions. From such an empirical analysis, one can generalize the mechanism as a radical-anion-covalent (C-M) triangle (Scheme 5.4). In any given case, the preferred mechanistic pathway may reside at some point within the triangle at a location determined by the substrate, the metal being used and the reaction conditions. The three corners represent the extremes situations.[7]



Scheme 5.4

In spite of the synthetic potential demonstrated by the aqueous indium-Barbier-type methodology in this dissertation, these reactions are still at an infant stage. The history of aqueous Barbier reactions is only a decade old, and the full synthetic capacity of this reaction still awaits exploration. Such reactions include the use of the hydrophobic effect of an aqueous environment to bring together the reactive functions in the construction of large carbocyclic rings (Scheme 5.5).

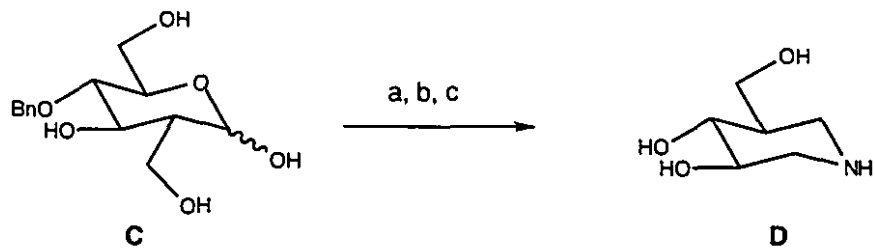


Scheme 5.5

By virtue of its higher reactivity, the indium-mediated reaction in water has found wide application in natural product synthesis. Synthetically, one of the most important features of carrying out organic reactions in water is that water-soluble hydroxyl-containing molecules can be used directly without involvement of protection-deprotection processes. As a result, the syntheses are usually made short and efficient. A typical such area is that of carbohydrate

chemistry. Several examples of this process have been demonstrated in the previous chapters.

Another important application of the newly developed diastereoselective synthesis of 2-substituted carbohydrates would be the convenient synthesis of the advanced intermediate **C** toward the synthesis Isofagomine **D**, a potent , new glycosidase inhibitor (Scheme 5.6).

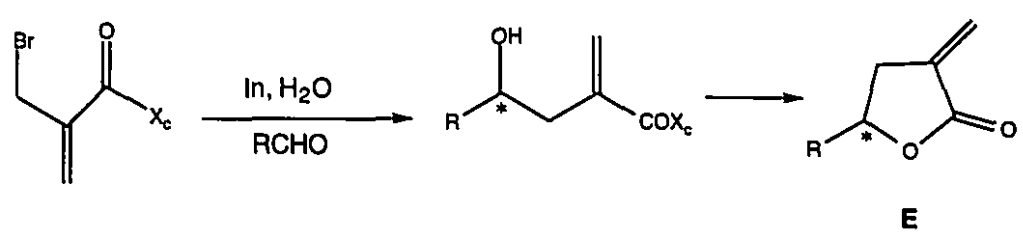


C **D**

a) $NaIO_4$, MeOH/H_2O 1:1, 45°C, 5h; b) NH_3/H_2O, H_2, Pd/C; c) H_2, Pd/C, HCl

Scheme 5.6

Enantioselective synthesis through such aqueous reactions, an area that will certainly be one of the most important development in the future, has not been fully explored. One aspect of the aqueous indium-mediated enantioselective coupling is targeted towards the synthesis of chiral α-methylene-γ-butyrolactones **E** (Scheme 5.7).



E

Scheme 5.7

In conclusion, the indium-mediated methodology in water as solvent seems to be showing great promise in organic chemistry. In addition, water can sometimes become an even more effective medium in that it can simultaneously

act as a solvent, a catalyst, and a reagent for reactions that are acid or base catalysed.[6] Water can also be used along with additives (such as Lithium chloride) which confer new properties and/or enhance hydrophobic effects. It also seems safe to predict that the use of water as a solvent for organic synthesis will become increasingly popular in the future. The need to reinforce the efforts for synthetic chemistry with less hazards and better environmental safety must mean the aqueous indium-promoted reactions merits a much closer look in terms of industrial development.

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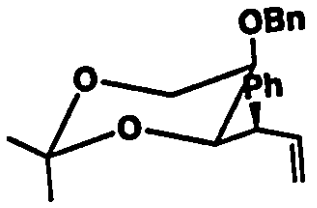
7. Li, C. J. J. Am. Chem. Soc. (in press).

Appendix


OBn
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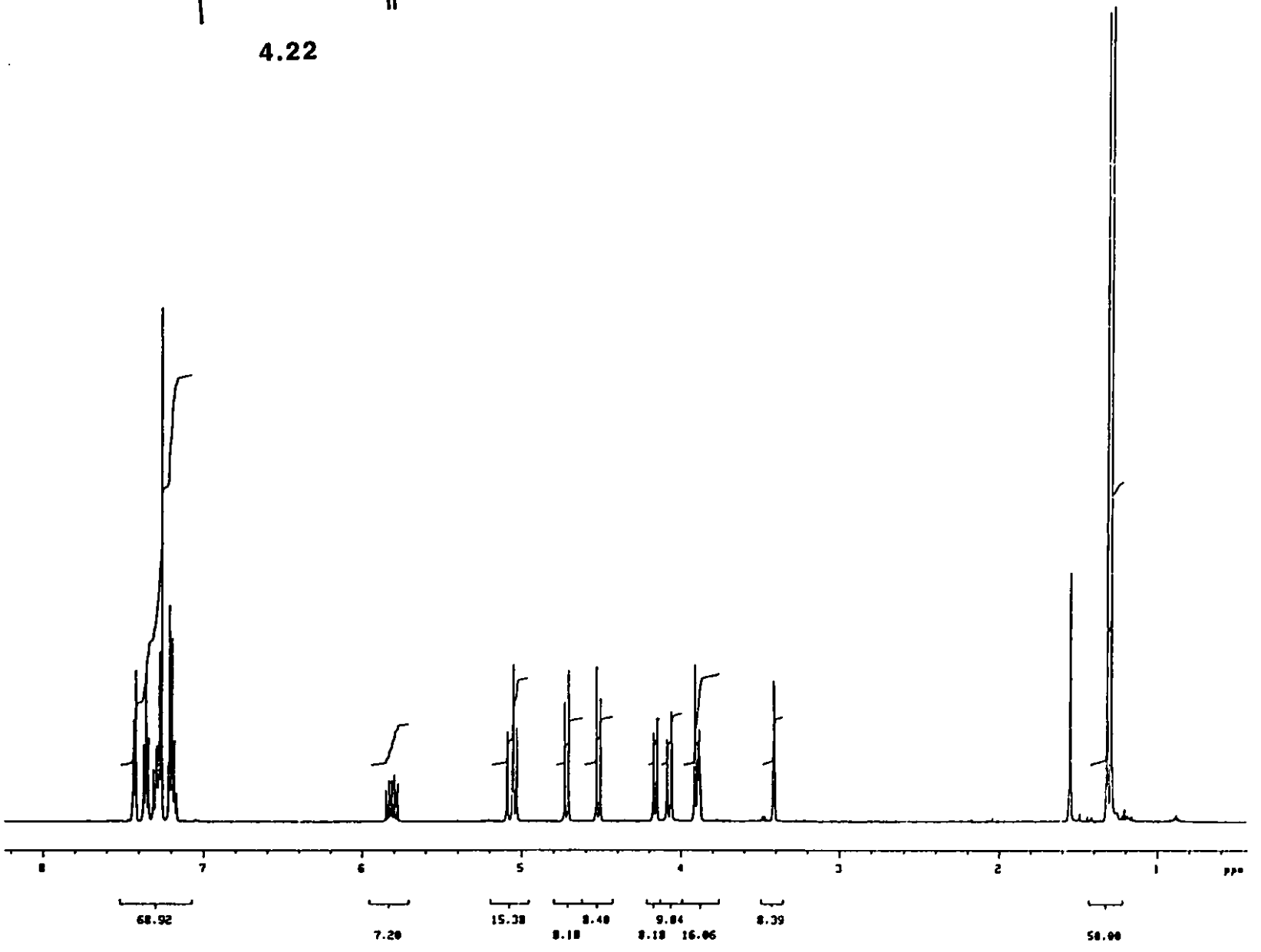
Ph
O

4.22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16.06
8.39
58.00

STA[redacted] PROTON PARAMETERS
S[redacted]FG probe
HI[redacted] is in file H1
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OBSERVE H1
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SPECTRAL WIDTH 3444.1 Hz
2D SPECTRAL WIDTH 3444.1 Hz
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RELAXATION DELAY 1.000 sec
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FIRST PULSE WIDTH 9.0 usec
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NO. INCREMENTS 574
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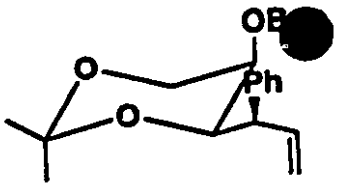

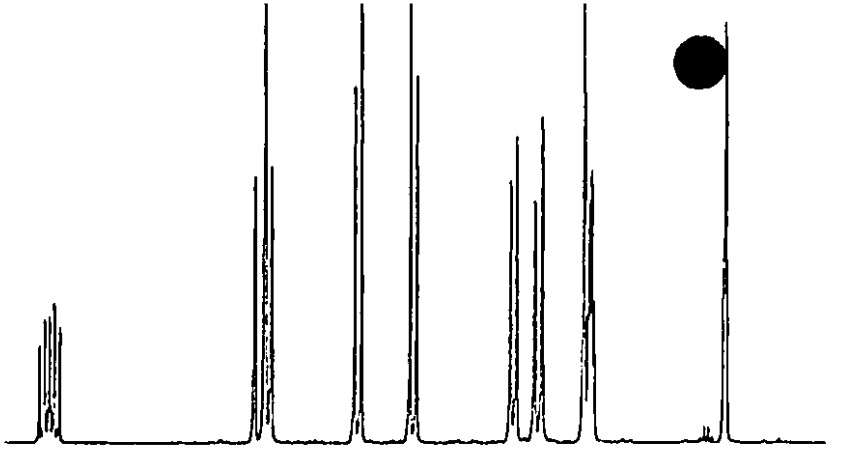

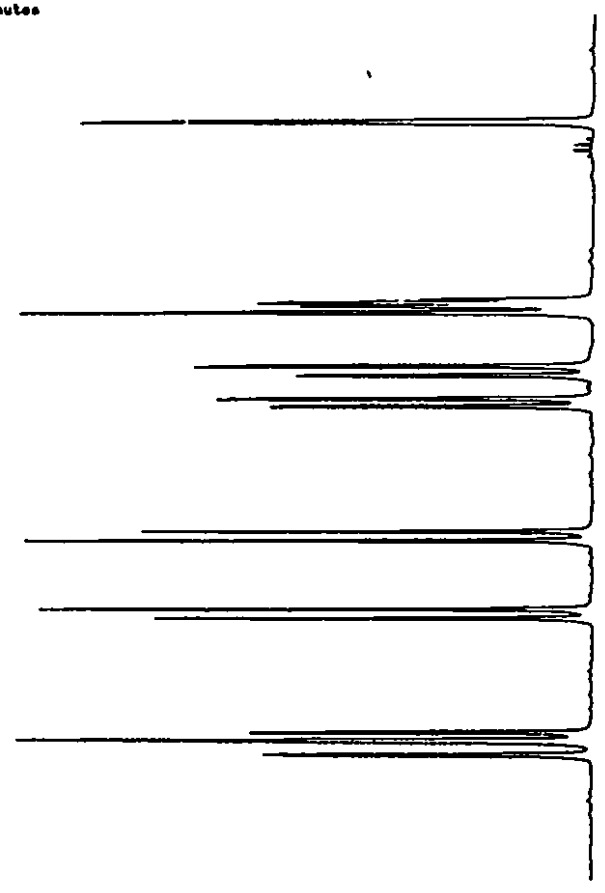

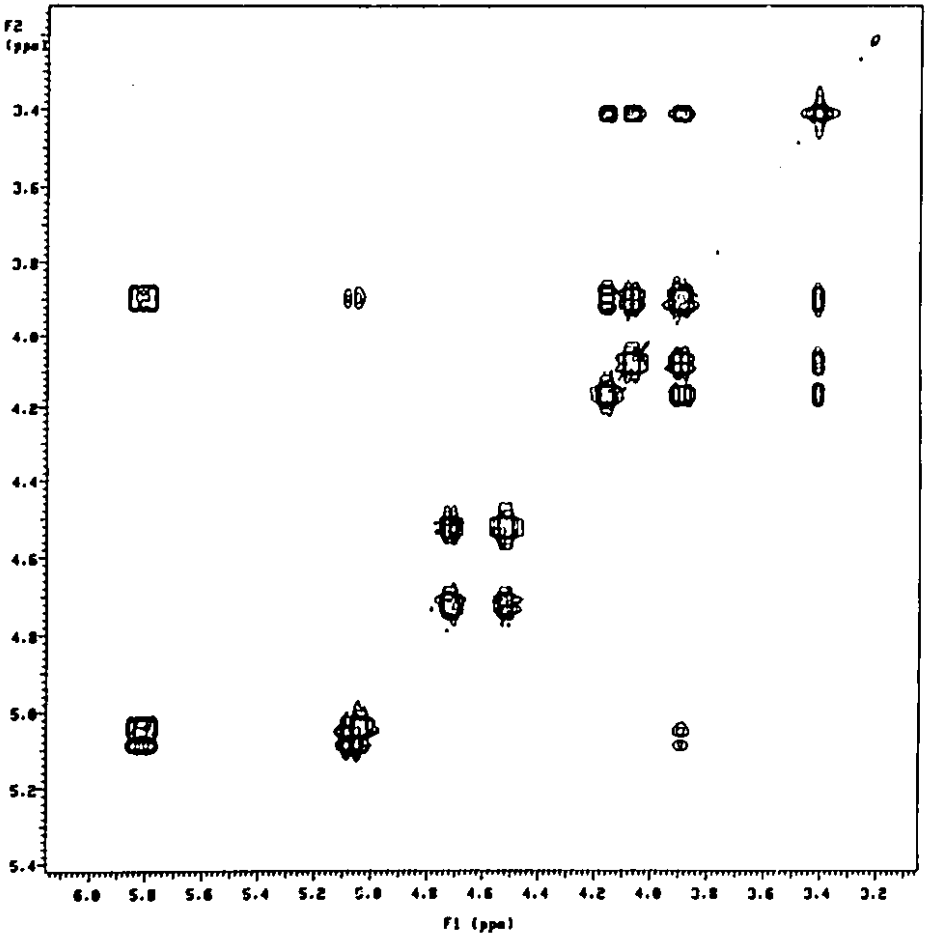

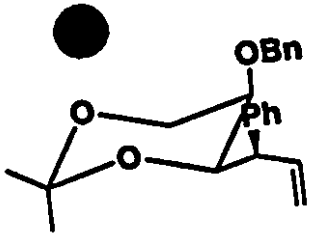
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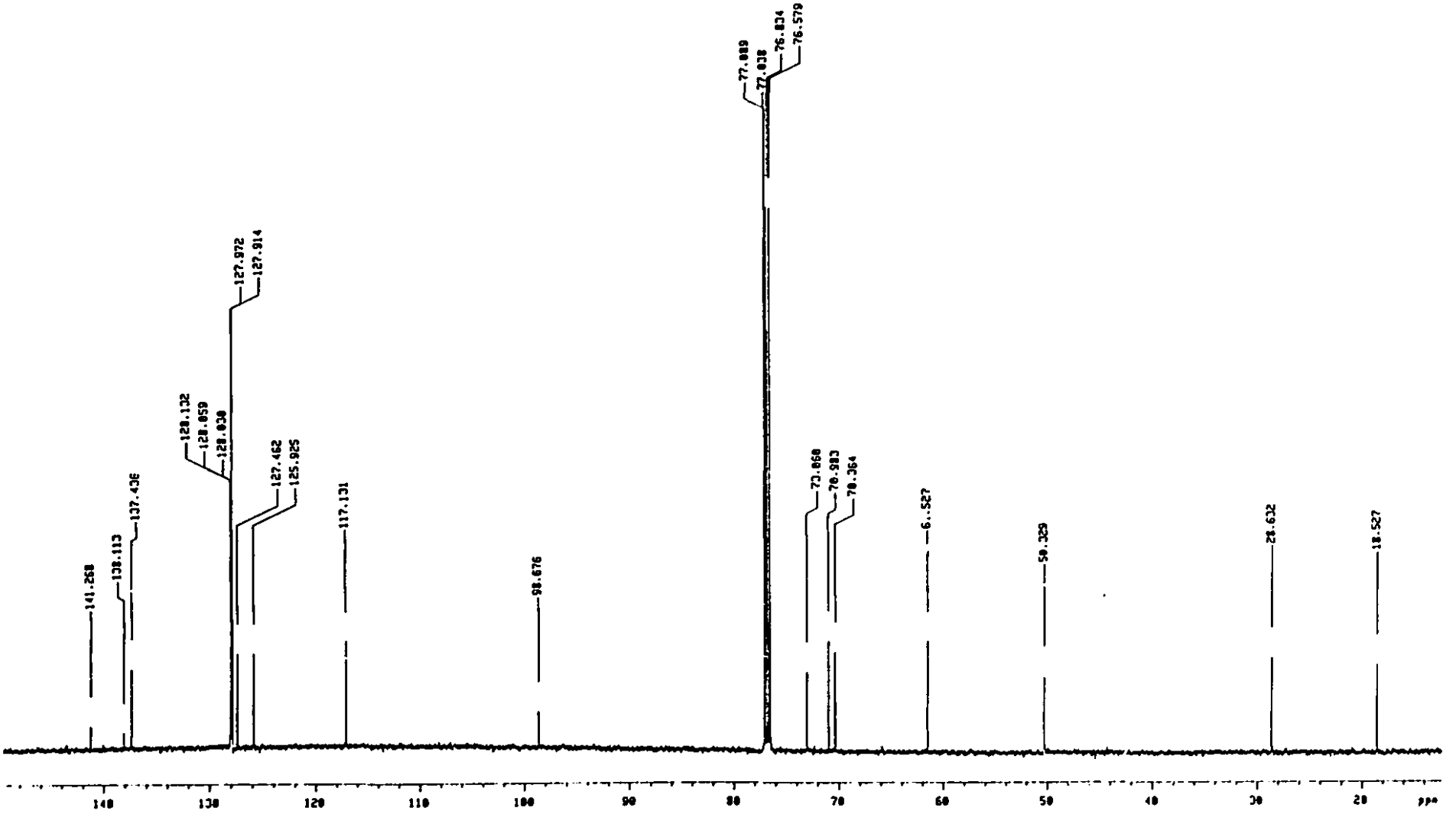
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120
110
100
90
80
70
60
50
40
30
20
ppm

STAN[illegible]ROTON PARAMETERS
5 mm [illegible]C probe
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2D SPECTRAL WIDTH 17597.6 Hz
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NO. INCREMENTS 256 X2
DECOUPLE C13
HIGH POWER 49
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DECOUPLER GATED OFF DURING DELAY
WALTZ-16 MODULATED
DOUBLE PRECISION ACQUISITION
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FT SIZE 1024
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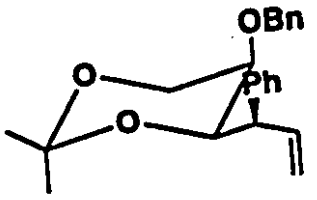
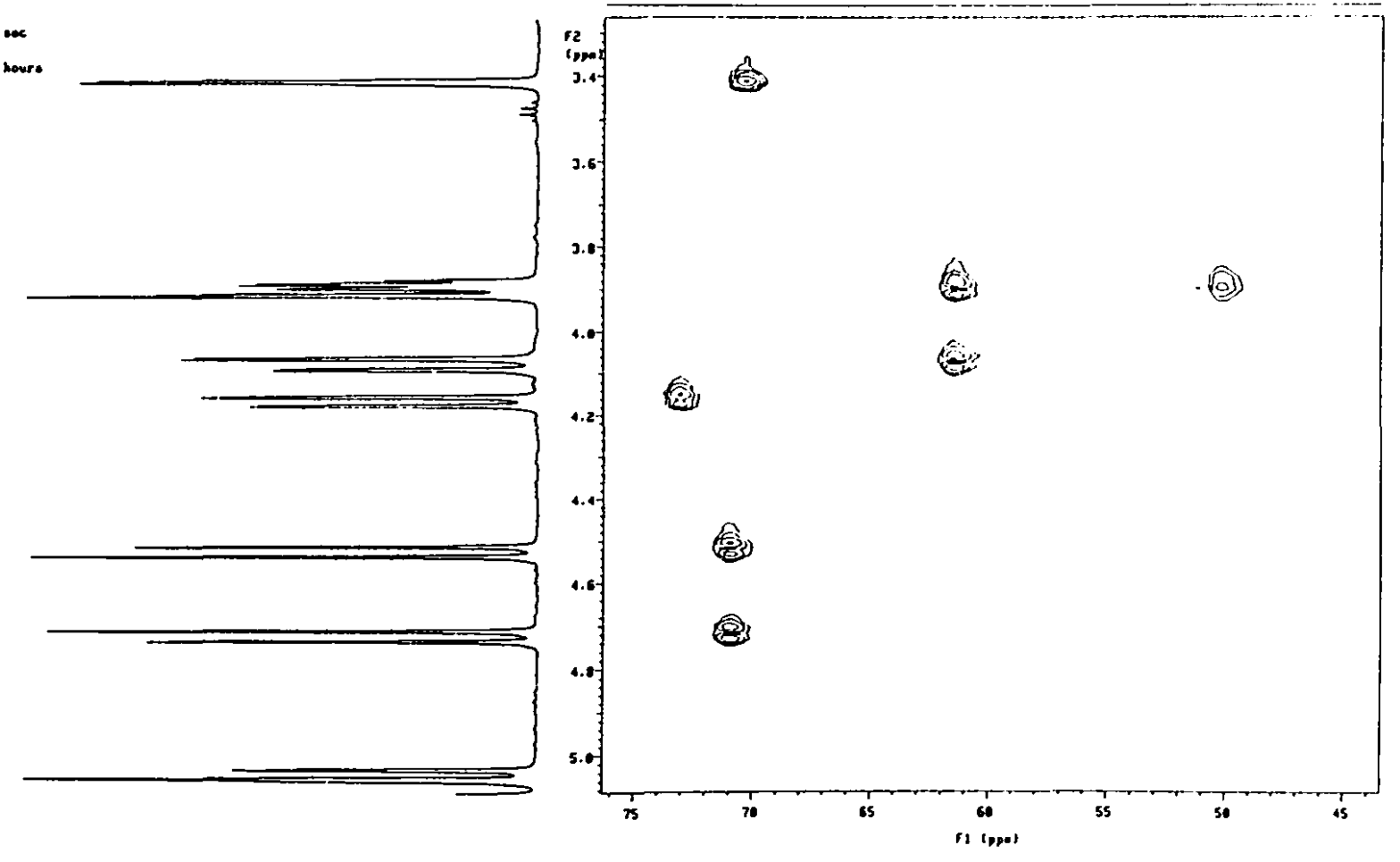




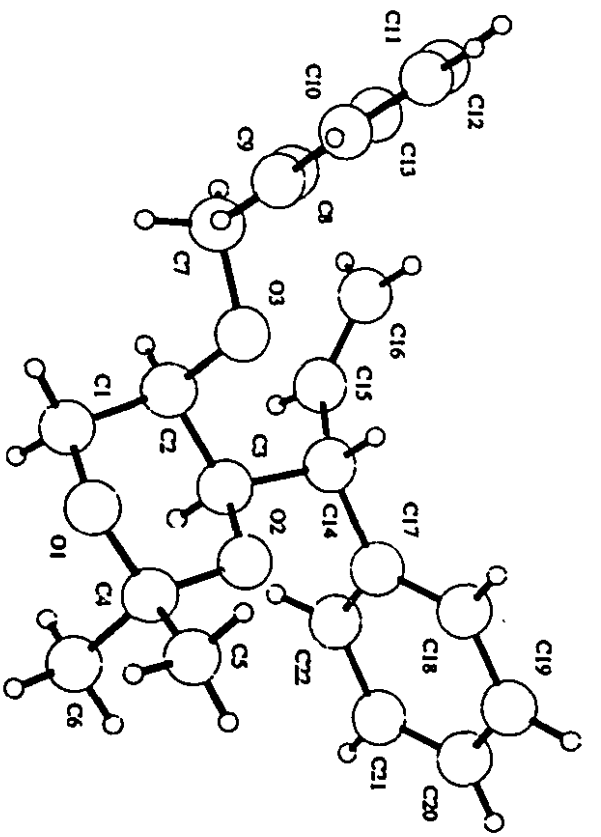


Fig 4.5a X-ray structure of **4.22**

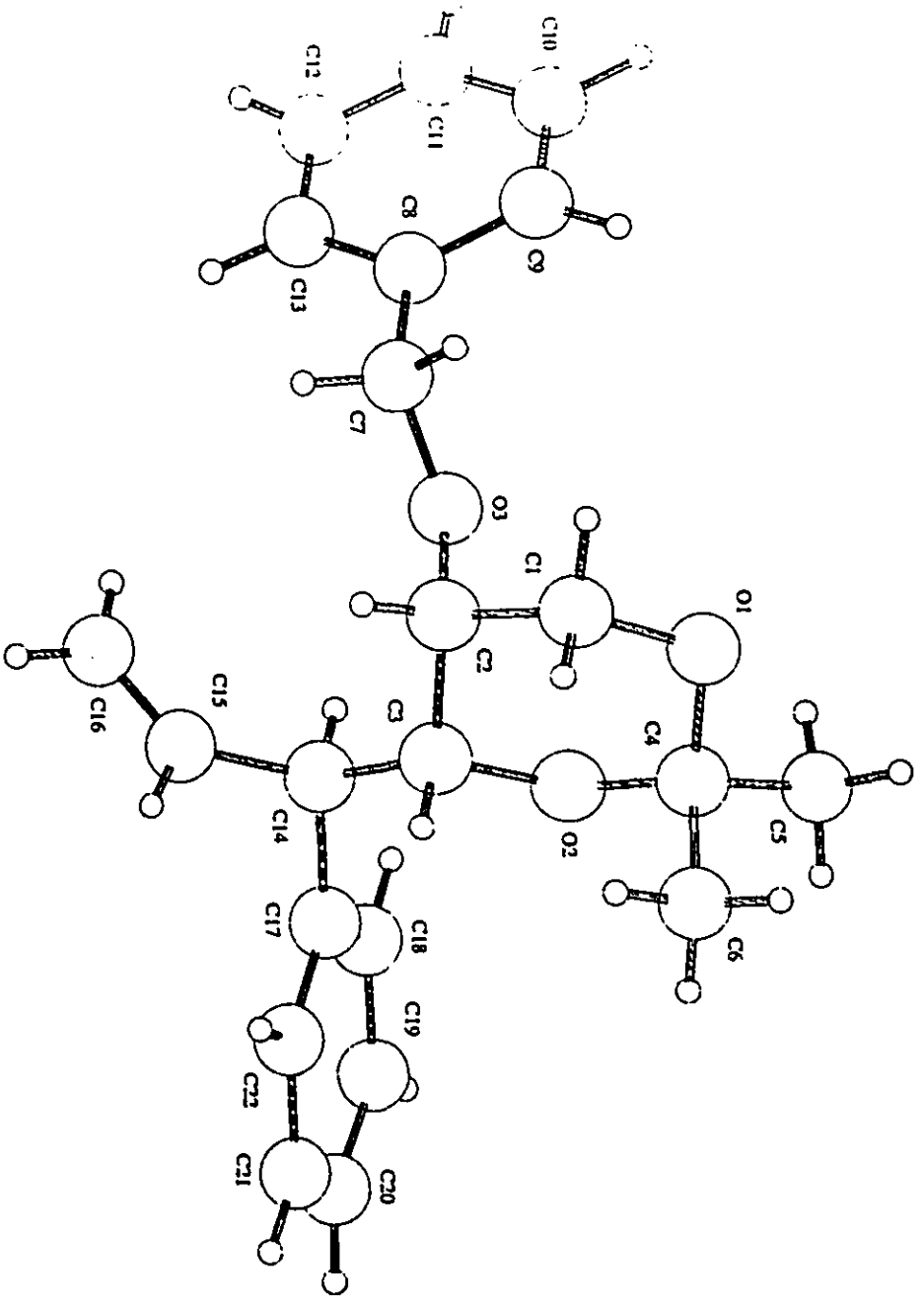


Fig 4.5b X-ray structure of **4.22**

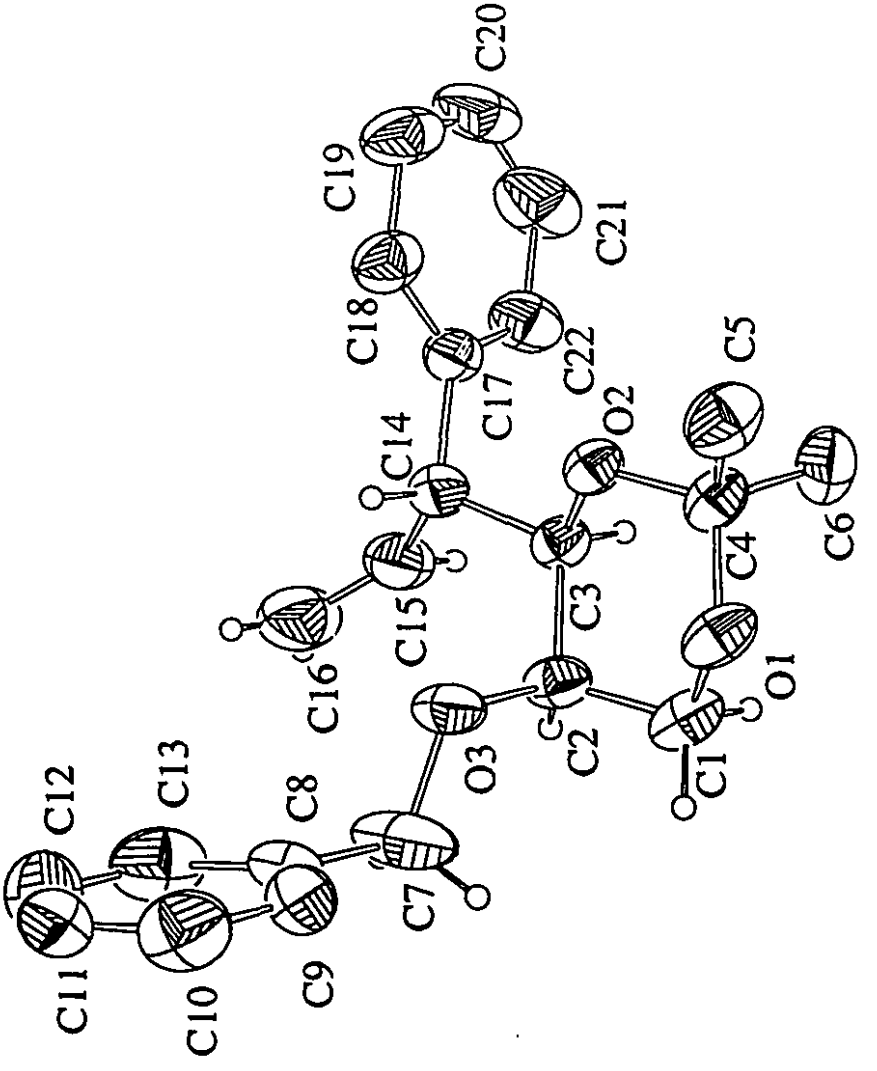
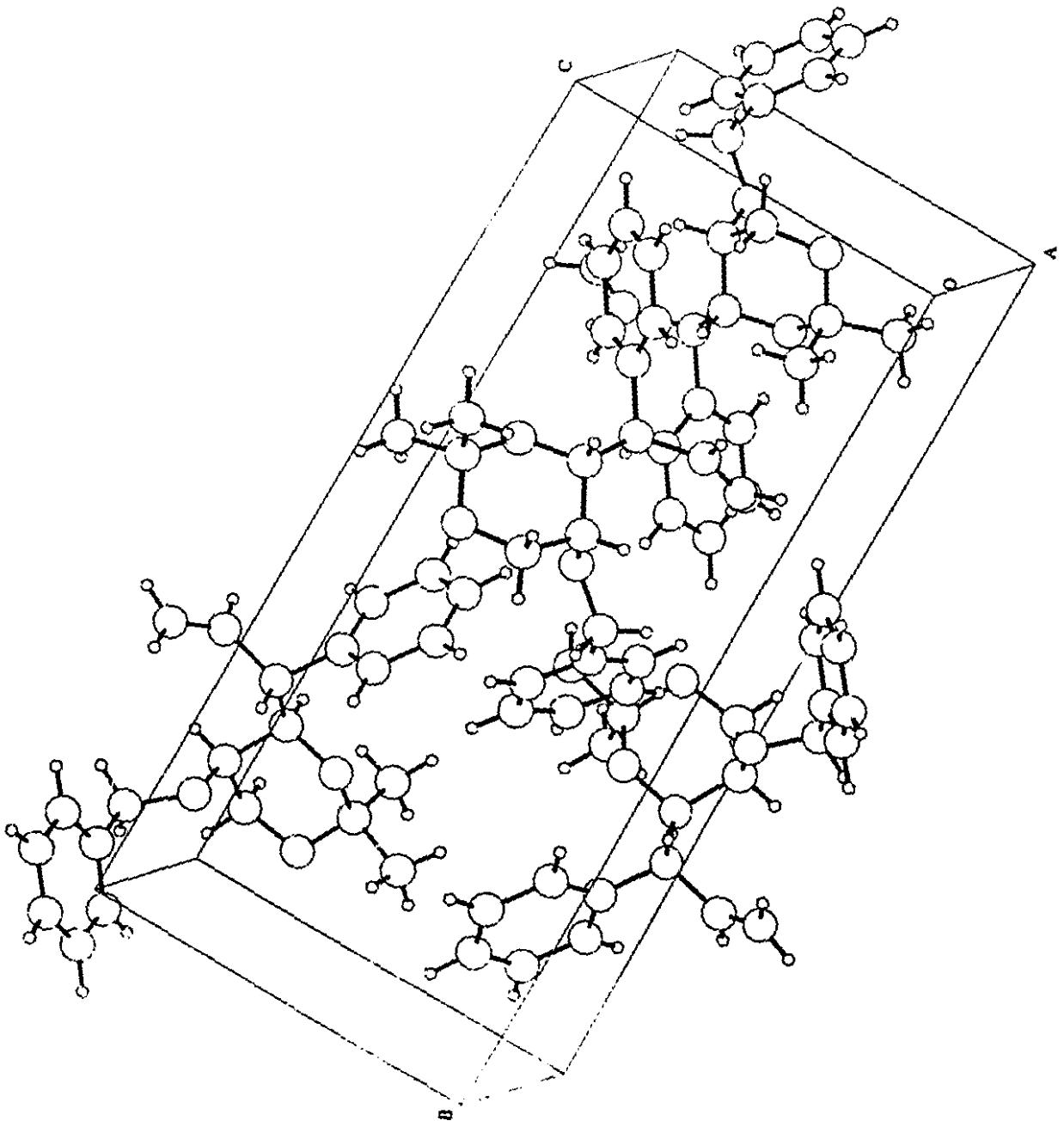


Fig 4.5c X-ray structure of **4.22**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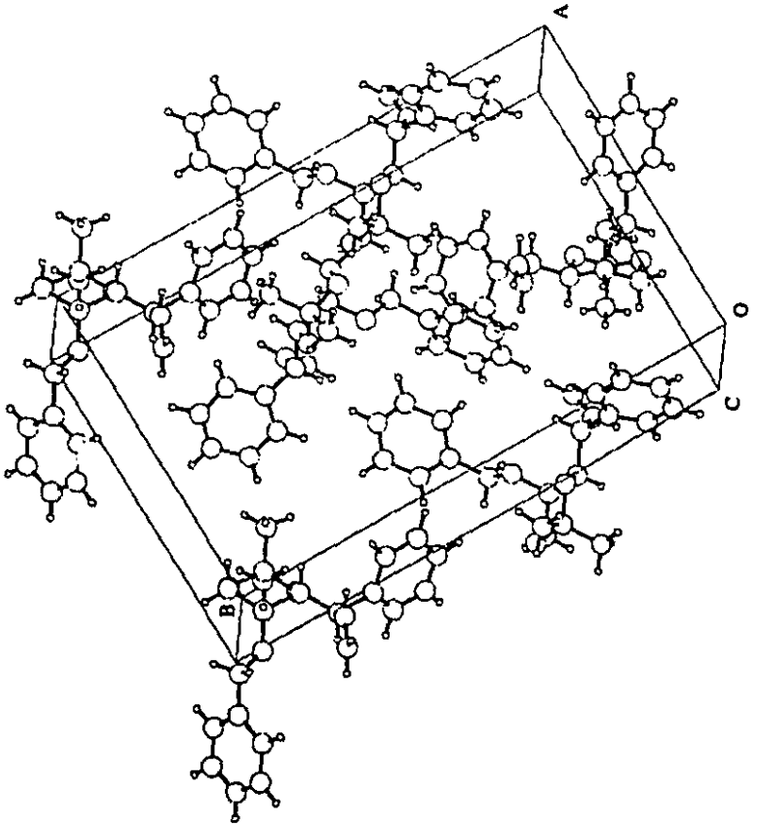
A
B


A
O
C
B

CHAN11B

Space Group and Cell Dimensions Orthorhombic P 212121
a 12.2461(19) b 19.1973(16) c 8.4399(17)
Volume 1984.2(5)A**3

Empirical formula : C22 H26 O3

Cell dimensions were obtained from 20 reflections with 2Theta angle
in the range 50.00 - 60.00 degrees.

Crystal dimensions : 0.50 X 0.30 X 0.20 mm

FW = 338.44 Z = 4 F(000) = 730.06

Dcalc 1.133Mg.m-3, mu 0.55mm-1, lambda 1.54056A, 2Theta(max) 120.0

The intensity data were collected on a Rigaku diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max 0 13; Kmin,max 0 21; Lmin,max 0 9
No. of reflections measured 11650
No. of unique reflections 2960
No. of reflections with Inet > 2.0sigma(Inet) 2658
Absorption corrections were made using empirical psi scans.
The minimum and maximum transmission factors are 0.806273 and 0.882313.

The last least squares cycle was calculated with
51 atoms, 227 parameters and 1534 out of 1717 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000100

The residuals are as follows :--
For significant reflections, RF 0.048, Rw 0.049 GoF 2.56
For all reflections, RF 0.056, Rw 0.050.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.075.

In the last D-map, the deepest hole was -0.130e/A**3,
and the highest peak 0.110e/A**3.

Secondary ext. coeff. = 1.625305 sigma = 0.137383

Data was collected over the whole shpere, equivalent reflections
were averaged (Rint 2.3%), Friedel mates were not. Standards remained
constant during data collection (variation was +- 0.4%). Structure was
solved by direct methods, carbon and oxygen atoms were refined
anisotropically, hydrogens were introduced in calculated positions.
The Absolute Structure of the Model was confirmed, based on 200 Measurements,
123 of which Support the Model. The Probability that the Above Statement
is WRONG is 0.7007E-03

The following references are relevant to the NRCVAX System.

1. Full System Reference :
   Gabe, E.J., Le Page, Y., Charland, J.-P., Lee, F.L. and White, P.S. (1989) J. Appl. Cryst., 22, 384-387.

2. Flack x Enantiomorph Refinement:
   Flack, H., (1983) Acta Cryst., A39, 876-881.

3. Scattering Factors from Int. Tab. Vol. 4 :
   International Tables for X-ray Crystallography, Vol. IV, (1974) Kynoch Press, Birmingham, England.

4. ORTEP Plotting :
   Johnson, C.K., (1976) ORTEP - A Fortran Thermal Ellipsoid Plot Program, Tehnical Report ORNL-5138, Oak Ridge

5. Extinction Treatment :
   Larson, A.C., (1970) p.293, Crystallographic Computing, Munksgaard, Copenhagen.

6. Missing Symmetry Treatment by MISSYM :
   Le Page, Y., (1988) J. Appl. Cryst., 21, 983-984.

7. Grouping of Equivalent Reflections in DATRD2 :
   Le Page, Y. and Gabe, E.J., (1979) J. Appl. Cryst., 12, 464-466.

8. Rogers Eta Enantiomorph Refinement:
   Rogers, D., (1981) Acta Cryst., A37, 734-741.

Table 1 Refined atomic coordinates and Beq for C22H26O3

Atom	x	y	z	Beq
O1	0.16983(19)	0.95245(11)	0.82942(36)	6.10(13)
O2	0.06354(17)	0.85162(10)	0.82651(28)	4.65(10)
O3	0.00319(18)	0.94246(11)	1.08313(29)	5.79(11)
C1	0.19234(32)	0.94365(19)	0.99392(55)	6.50(20)
C2	0.10210(30)	0.90389(18)	1.07737(46)	5.36(17)
C3	0.08307(27)	0.83648(16)	0.98907(42)	4.60(16)
C4	0.14815(30)	0.88919(17)	0.74985(49)	5.45(18)
C5	0.10206(35)	0.91034(22)	0.59155(55)	7.19(22)
C6	0.25143(32)	0.84489(21)	0.73250(57)	7.36(23)
C7	-0.00115(49)	0.99055(25)	1.21034(67)	10.45(31)
C8	-0.10356(35)	1.03140(19)	1.20417(46)	5.59(19)
C9	-0.11323(33)	1.08790(23)	1.10822(50)	6.47(20)
C10	-0.20700(48)	1.12674(23)	1.10232(72)	8.60(29)
C11	-0.29189(45)	1.10760(35)	1.19154(97)	9.73(37)
C12	-0.28676(59)	1.05383(47)	1.28772(85)	11.13(43)
C13	-0.19260(63)	1.01418(25)	1.29459(67)	9.03(32)
C14	-0.01281(30)	0.79324(17)	1.04741(43)	5.29(17)
C15	-0.00228(44)	0.77526(23)	1.21914(54)	7.59(24)
C16	-0.06770(52)	0.79255(30)	1.32833(70)	11.31(36)
C17	-0.02552(31)	0.72781(17)	0.94772(42)	5.11(17)
C18	-0.11244(35)	0.72090(20)	0.84591(52)	6.61(20)
C19	-0.12315(52)	0.66109(34)	0.75263(58)	9.13(31)
C20	-0.04886(71)	0.60879(29)	0.76656(74)	10.09(40)
C21	0.03604(58)	0.61526(24)	0.86437(79)	10.30(38)
C22	0.04824(38)	0.67447(21)	0.95637(55)	7.49(24)

Table 2 Calculated hydrogen atom coordinates for C22H26O3

Atom	x	y	z	Biso
H1A	0.2586	0.9184	1.0045	7.3
H1B	0.2000	0.9882	1.0416	7.3
H2	0.1260	0.8933	1.1818	6.1
H3	0.1472	0.8089	0.9975	5.3
H5A	0.0896	0.8704	0.5280	7.9
H5B	0.1513	0.9409	0.5394	7.9
H5C	0.0349	0.9339	0.6104	7.9
H6A	0.2792	0.8353	0.8355	8.1
H6B	0.3041	0.8710	0.6745	8.1
H6C	0.2361	0.8028	0.6787	8.1
H7A	0.0033	0.9666	1.3082	11.3
H7B	0.0586	1.0219	1.2002	11.3
H9	-0.0530	1.1012	1.0443	7.2
H10	-0.2118	1.1662	1.0353	9.4
H11	-0.3568	1.1339	1.1813	10.6
H12	-0.3501	1.0449	1.3488	12.0
H13	-0.1920	0.9755	1.3639	9.9
H14	-0.0769	0.8202	1.0349	6.1
H15	0.0590	0.7480	1.2484	8.4
H16B	-0.0412	0.7740	1.4243	12.5
H16A	-0.1329	0.8194	1.3186	12.5
H18	-0.1653	0.7567	0.8385	7.5
H19	-0.1809	0.6559	0.6789	10.0
H20	-0.0556	0.5671	0.7073	11.0
H21	0.0893	0.5798	0.8733	11.2
H22	0.1083	0.6784	1.0264	8.4

C-H distance is 0.95A, Biso(H)= 1.1 x Beq(C)

Table 3 Anisotropic thermal parameters for C22H26O3

Atom	u11	u22	u33	u12	u13	u23
O1	7.85(16)	5.24(14)	10.07(20)	-1.33(13)	-2.66(16)	1.29(15)
O2	5.88(13)	4.92(12)	6.88(15)	-0.58(11)	-0.65(12)	0.23(12)
O3	7.67(15)	6.00(13)	8.32(17)	1.41(13)	-2.43(15)	-2.35(14)
C1	7.8(3)	5.9(2)	11.1(3)	-1.0(2)	-3.1(3)	0.2(3)
C2	6.9(2)	5.8(2)	7.6(3)	0.4(2)	-2.2(2)	-0.9(2)
C3	5.7(2)	4.6(2)	7.2(2)	0.2(2)	-0.9(2)	-0.1(2)
C4	6.3(2)	5.6(2)	8.8(3)	-1.0(2)	-0.9(2)	0.8(2)
C5	9.9(3)	8.6(3)	8.8(3)	-2.2(3)	-1.2(3)	1.9(3)
C6	7.2(2)	8.8(3)	11.9(4)	0.1(2)	1.2(3)	0.7(3)
C7	15.1(4)	11.1(3)	13.5(5)	5.3(3)	-6.6(4)	-6.8(4)
C8	9.4(3)	5.6(2)	6.3(2)	0.7(2)	-0.7(2)	-1.5(2)
C9	8.3(3)	9.0(3)	7.3(3)	-0.7(2)	1.0(2)	-0.7(3)
C10	11.2(4)	7.7(3)	13.8(4)	1.1(3)	-2.7(4)	0.2(3)
C11	8.1(3)	12.3(5)	16.6(7)	0.8(4)	-0.2(4)	-7.3(5)
C12	12.3(5)	16.9(6)	13.0(6)	-5.0(5)	5.4(5)	-4.1(5)
C13	16.8(6)	8.0(3)	9.4(4)	-3.2(4)	0.4(4)	1.4(3)
C14	7.1(2)	5.8(2)	7.1(2)	-0.7(2)	0.3(2)	-0.8(2)
C15	12.2(4)	9.0(3)	7.6(3)	-3.1(3)	2.0(3)	-1.6(3)
C16	17.7(6)	14.3(5)	11.0(4)	-7.5(4)	4.1(4)	-3.4(4)
C17	7.7(2)	5.4(2)	6.3(2)	-1.7(2)	1.1(2)	0.0(2)
C18	9.4(3)	8.2(3)	7.5(3)	-2.8(2)	-0.1(3)	0.6(2)
C19	14.9(5)	12.7(4)	7.0(3)	-8.1(4)	0.8(3)	-0.7(4)
C20	21.3(8)	8.4(3)	8.6(4)	-6.5(4)	5.0(5)	-3.0(3)
C21	19.4(6)	6.2(3)	13.5(5)	-0.6(4)	3.2(5)	-1.7(3)
C22	12.4(4)	6.3(2)	9.8(3)	0.6(3)	0.4(3)	-1.0(3)
H1A	9.2					
H1B	9.2					
H2	7.7					
H3	6.8					
H5A	10.1					
H5B	10.1					
H5C	10.1					
H6A	10.3					
H6B	10.3					
H6C	10.3					
H7A	14.3					
H7B	14.3					
H9	9.1					
H10	11.9					
H11	13.4					
H12	15.3					
H13	12.5					
H14	7.8					
H15	10.7					
H16B	15.9					
H16A	15.9					
H18	9.4					
H19	12.6					
H20	14.0					
H21	14.2					
H22	10.6					

Temp=-2(Pi)**2(u11*h*h*astar*astar+---+2*u12*h*k*astar*bstar+---)

The uij values have been multiplied by 100.

Table 4 Distances for C22H2603

O(1)-C(1)	1.426(5)	C(9)-C(10)	1.370(7)
O(1)-C(4)	1.413(4)	C(10)-C(11)	1.335(10)
O(2)-C(3)	1.423(4)	C(11)-C(12)	1.315(13)
O(2)-C(4)	1.419(4)	C(12)-C(13)	1.383(12)
O(3)-C(2)	1.420(4)	C(14)-C(15)	1.495(6)
O(3)-C(7)	1.417(5)	C(14)-C(17)	1.520(5)
C(1)-C(2)	1.516(6)	C(15)-C(16)	1.265(8)
C(2)-C(3)	1.511(5)	C(17)-C(18)	1.374(6)
C(3)-C(14)	1.520(5)	C(17)-C(22)	1.367(6)
C(4)-C(5)	1.506(6)	C(18)-C(19)	1.398(7)
C(4)-C(6)	1.531(5)	C(19)-C(20)	1.360(12)
C(7)-C(8)	1.480(6)	C(20)-C(21)	1.333(12)
C(8)-C(9)	1.359(6)	C(21)-C(22)	1.385(7)
C(8)-C(13)	1.371(9)		

Table 5 Angles for C22H2603

C(1)-O(1)-C(4)	113.4(3)	C(9)-C(8)-C(13)	117.1(4)
C(3)-O(2)-C(4)	114.90(25)	C(8)-C(9)-C(10)	121.9(4)
C(2)-O(3)-C(7)	113.4(3)	C(9)-C(10)-C(11)	118.8(5)
O(1)-C(1)-C(2)	111.8(3)	C(10)-C(11)-C(12)	121.8(5)
O(3)-C(2)-C(1)	112.0(3)	C(11)-C(12)-C(13)	119.9(5)
O(3)-C(2)-C(3)	109.4(3)	C(8)-C(13)-C(12)	120.5(5)
C(1)-C(2)-C(3)	108.3(3)	C(3)-C(14)-C(15)	111.9(3)
O(2)-C(3)-C(2)	109.1(3)	C(3)-C(14)-C(17)	110.6(3)
O(2)-C(3)-C(14)	107.1(3)	C(15)-C(14)-C(17)	110.8(3)
C(2)-C(3)-C(14)	115.3(3)	C(14)-C(15)-C(16)	126.2(5)
O(1)-C(4)-O(2)	110.9(3)	C(14)-C(17)-C(18)	120.3(3)
O(1)-C(4)-C(5)	105.1(3)	C(14)-C(17)-C(22)	121.4(4)
O(1)-C(4)-C(6)	111.6(3)	C(18)-C(17)-C(22)	118.2(4)
O(2)-C(4)-C(5)	105.5(3)	C(17)-C(18)-C(19)	120.3(5)
O(2)-C(4)-C(6)	111.4(3)	C(18)-C(19)-C(20)	119.7(5)
C(5)-C(4)-C(6)	112.0(4)	C(19)-C(20)-C(21)	120.4(5)
O(3)-C(7)-C(8)	110.5(4)	C(20)-C(21)-C(22)	120.5(5)
C(7)-C(8)-C(9)	121.2(5)	C(17)-C(22)-C(21)	120.9(5)
C(7)-C(8)-C(13)	121.8(5)		

Table 6 . Distances(A) to the least-squares planes for C22H2603

Plane no. 1

Equation of the plane : 4.18(3)X + 11.22(4)Y + 6.215(16)Z = 18.62(3)

Distances(A) to the plane from the atoms in the plane.

C8	0.001(6)	C9	-0.002(6)
C10	0.005(7)	C11	-0.009(10)
C12	0.007(11)	C13	-0.002(9)

Chi squared for this plane 2.053

Plane no. 2

Equation of the plane : 6.602(23)X + 8.15(4)Y - 6.138(14)Z = 0.05(4)

Distances(A) to the plane from the atoms in the plane.

C17	0.001(5)	C18	-0.004(6)
C19	0.010(8)	C20	-0.012(10)
C21	0.001(8)	C22	0.000(6)

Chi squared for this plane 3.551

Dihedral angle between planes A and B

A	B	Angle(deg)
1	2	95.94(21)

Table 7 Torsion angles C22H2603

C4	O1	C1	C2	-54.4(3)	C1	O1	C4	O2	53.9(2)
C1	O1	C4	C5	167.5(4)	C1	O1	C4	C6	-71.0(3)
C4	O2	C3	C2	57.5(3)	C4	O2	C3	C14	-177.1(4)
C3	O2	C4	O1	-56.7(2)	C3	O2	C4	C5	-170.0(4)
C3	O2	C4	C6	68.2(3)	C7	O3	C2	C1	-83.4(4)
C7	O3	C2	C3	156.5(4)	C2	O3	C7	C8	177.0(5)
O1	C1	C2	O3	-67.3(3)	O1	C1	C2	C3	53.4(3)
O3	C2	C3	O2	68.6(3)	O3	C2	C3	C14	-51.9(2)
C1	C2	C3	O2	-53.7(2)	C1	C2	C3	C14	-174.2(4)
O2	C3	C14	C15	-178.9(4)	O2	C3	C14	C17	57.1(2)
C2	C3	C14	C15	-57.3(3)	C2	C3	C14	C17	178.7(4)
O3	C7	C8	C9	-82.1(4)	O3	C7	C8	C13	97.9(5)
C7	C8	C9	C10	-179.3(6)	C13	C8	C9	C10	0.6(3)
C7	C8	C13	C12	179.2(7)	C9	C8	C13	C12	-0.7(4)
C8	C9	C10	C11	-1.2(3)	C9	C10	C11	C12	1.9(4)
C10	C11	C12	C13	-2.0(3)	C11	C12	C13	C8	1.4(3)
C3	C14	C15	C16	118.8(5)	C17	C14	C15	C16	-117.3(5)
C3	C14	C17	C18	-109.6(4)	C3	C14	C17	C22	70.5(3)
C15	C14	C17	C18	125.7(4)	C15	C14	C17	C22	-54.2(3)
C14	C17	C18	C19	179.1(5)	C22	C17	C18	C19	-1.0(3)
C14	C17	C22	C21	-179.7(5)	C18	C17	C22	C21	0.4(3)
C17	C18	C19	C20	2.0(3)	C18	C19	C20	C21	-2.4(3)
C19	C20	C21	C22	1.8(3)	C20	C21	C22	C17	-0.8(3)

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	0, 0, 1			5	30	29	2	7	16	4	4		0, 17, 1		
2	756	846	1	6	136	134	1	8	4	1	15*	1	138	139	2
4	274	263	1	7	83	72	2		0, 11, 1			2	59	62	2
[illegible]	53	41	2	8	55	61	2	1	171	169	1	3	13	0	5*
[illegible]	45	44	3	9	23	10	3	2	139	138	1	4	13	12	5*
	0, 1, 1				0, 6, 1			3	4	1	13*	5	5	7	13*
1	795	984	1	0	162	173	1	4	60	62	2		0, 18, 1		
2	689	770	1	1	296	301	1	5	70	71	2	0	180	190	2
3	180	189	1	2	226	223	1	6	32	24	3	1	82	75	2
4	461	449	1	3	316	310	1	7	22	17	3	2	18	23	5*
5	188	183	1	4	291	284	1	8	4	2	16*	3	25	21	3
6	12	11	4*	5	133	131	1		0, 12, 1			4	55	57	2
7	20	14	3	6	156	162	1	0	120	120	2	5	28	20	2
8	89	96	2	7	25	24	3	1	14	4	3		0, 19, 1		
9	24	37	4	8	5	3	19*	2	102	96	1	1	58	61	2
	0, 2, 1			9	22	12	3	3	39	30	2	2	18	14	4
0	389	399	1		0, 7, 1			4	73	72	2	3	32	22	2
1	471	517	1	1	503	500	1	5	43	54	2	4	30	32	2
2	354	382	1	2	381	378	1	6	44	49	2		0, 20, 1		
3	179	181	1	3	141	134	1	7	22	28	4	0	55	51	2
4	100	95	1	4	200	188	1		0, 13, 1			1	47	45	2
5	183	190	1	5	26	25	3	1	96	96	1	2	24	17	2
6	61	54	2	6	33	32	2	2	14	7	4*	3	43	40	2
7	34	30	2	7	42	40	2	3	79	81	1		0, 21, 1		
8	7	7	11*	8	14	1	6*	4	33	30	2	1	51	54	2
9	16	18	5*		0, 8, 1			5	12	5	5*	2	31	35	2
	0, 3, 1			0	73	72	1	6	20	20	4		1, 0, 1		
1	83	83	1	1	614	610	1	7	12	14	6*	1	156	165	1
2	383	381	1	2	482	467	1		0, 14, 1			2	116	121	1
3	89	87	1	3	13	23	3*	0	32	32	4	3	145	148	1
[illegible]	117	116	1	4	16	11	4	1	7	3	10*	4	32	19	1
5	80	75	1	5	95	91	1	2	24	26	3	5	87	89	1
6	45	41	2	6	36	36	2	3	44	35	2	6	42	37	2
7	5	24	21*	7	144	149	2	4	60	64	2	7	44	42	2
8	5	0	14*	8	22	14	4	5	18	7	4	8	13	27	8*
9	18	2	4		0, 9, 1			6	33	36	3	9	62	66	3
	0, 4, 1			1	7	1	5*	7	16	10	3		1, 1, 1		
0	595	633	1	2	444	448	1		0, 15, 1			0	229	238	0
1	754	805	1	3	212	213	1	1	51	48	2	1	501	525	1
2	11	14	3	4	171	170	1	2	46	41	2	2	504	532	1
3	94	96	1	5	23	22	3	3	29	28	3	3	147	150	1
4	43	41	1	6	75	72	2	4	33	22	2	4	239	244	1
5	32	32	2	7	32	36	3	5	55	58	2	5	59	55	1
6	97	95	2	8	24	21	3	6	54	57	2	6	24	22	3
7	64	56	2		0, 10, 1				0, 16, 1			7	58	57	2
8	66	73	2	0	95	109	2	0	130	139	2	8	75	74	3
9	31	16	3	1	20	11	2	1	45	41	2	9	20	2	5
	0, 5, 1			2	4	6	11*	2	54	52	2		1, 2, 1		
1	334	338	1	3	50	45	1	3	58	62	2	0	509	549	1
2	499	511	1	4	38	33	2	4	19	25	4	1	578	641	1
3	87	91	1	5	13	13	5*	5	21	19	3	2	221	234	1
4	11	5	4*	6	99	108	2	6	4	5	15*	3	222	226	1

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	1, 2, 1			0	101	100	1	2	129	123	1	4	23	10	3
4	122	130	1	1	160	161	1	3	59	57	2	5	41	43	2
5	78	79	1	2	229	224	1	4	52	44	2		1, 19, 1		
6	66	66	2	3	249	247	1	5	84	88	2	0	109	118	2
7	36	36	3	4	150	149	1	6	36	32	2	1	91	92	2
8	48	48	3	5	121	120	1	7	52	49	2	2	22	20	3
9	30	15	2	6	61	59	2		1, 13, 1			3	33	36	3
	1, 3, 1			7	64	62	2	0	110	108	1	4	84	85	2
0	511	531	1	8	28	18	3	1	101	96	1		1, 20, 1		
1	222	230	1		1, 8, 1			2	20	10	2	0	44	43	2
2	612	646	1	0	77	76	1	3	91	95	1	1	29	28	3
3	172	180	1	1	107	109	1	4	98	100	2	2	31	34	2
4	385	393	1	2	80	84	1	5	36	35	2	3	83	83	2
5	61	58	1	3	156	145	1	6	43	43	2		1, 21, 1		
6	53	58	2	4	88	87	1	7	10	21	8*	0	47	44	2
7	51	49	2	5	30	32	2		1, 14, 1			1	40	38	2
8	31	17	3	6	103	111	2	0	88	89	1	2	32	35	2
9	34	23	3	7	22	29	3	1	65	60	2		2, 0, 1		
	1, 4, 1			8	26	17	3	2	66	67	2	0	847	971	1
0	212	208	1		1, 9, 1			3	44	38	2	1	316	342	1
1	927	1024	1	0	303	308	1	4	42	43	2	2	378	398	1
2	435	451	1	1	313	305	1	5	55	54	2	3	34	34	1
3	448	456	1	2	237	233	1	6	22	20	3	4	69	71	1
4	127	122	1	3	121	124	1	7	20	21	3	5	222	235	1
5	90	89	1	4	12	26	4*		1, 15, 1			6	71	75	1
6	146	147	1	5	24	27	3	0	77	78	2	7	58	54	2
7	27	18	3	6	81	74	2	1	78	84	2	8	41	51	2
8	31	23	3	7	36	40	3	2	18	19	4	9	37	33	3
9	15	7	6*	8	15	14	5*	3	25	20	3		2, 1, 1		
	1, 5, 1				1, 10, 1			4	15	9	4*	0	376	383	1
0	124	124	1	0	139	135	1	5	38	32	2	1	1027	1202	1
1	263	262	1	1	170	160	1	6	28	29	3	2	683	726	1
2	186	193	1	2	186	187	1		1, 16, 1			3	157	158	1
3	167	169	1	3	110	104	1	0	59	64	2	4	33	27	2
4	172	179	1	4	80	80	1	1	59	55	2	5	58	64	1
5	144	145	1	5	49	55	2	2	41	37	2	6	86	86	2
6	58	57	2	6	25	23	3	3	43	43	2	7	69	75	2
7	36	38	2	7	74	78	2	4	34	37	2	8	46	44	2
8	24	29	4	8	20	17	4	5	41	38	2	9	6	13	15*
9	41	31	2		1, 11, 1			6	22	15	3		2, 2, 1		
	1, 6, 1			0	139	141	1		1, 17, 1			0	674	723	1
0	433	443	1	1	139	139	1	0	10	25	7*	1	933	1058	1
1	72	74	1	2	73	73	1	1	82	81	2	2	334	342	1
2	58	61	1	3	88	92	1	2	52	48	2	3	81	82	1
3	186	179	1	4	27	28	2	3	23	22	3	4	343	346	1
4	102	108	1	5	59	58	2	4	51	54	2	5	176	179	1
5	66	64	1	6	93	84	2	5	18	20	3	6	105	100	1
6	68	68	2	7	59	53	2		1, 18, 1			7	43	38	2
7	41	36	2	8	27	32	3	0	125	125	2	8	66	70	2
8	30	32	3		1, 12, 1			1	59	59	2	9	44	32	2
9	15	8	4*	0	222	222	1	2	59	54	2		2, 3, 1		
	1, 7, 1			1	95	89	1	3	44	47	2	0	1170	1367	1

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	2, 3, 1			8	35	27	2	1	46	48	2		2, 20, 1		
1	287	295	1		2, 8, 1			2	50	52	2	0	16	12	4*
2	398	401	1	0	17	17	2	3	104	104	1	1	71	80	2
3	222	228	1	1	224	216	1	4	48	39	2	2	25	27	3
4	392	395	1	2	350	337	1	5	82	80	2	3	50	49	2
5	164	163	1	3	128	126	1	6	35	37	2		2, 21, 1		
6	10	18	7*	4	117	113	1	7	29	21	3	0	4	17	14*
7	17	18	5*	5	39	43	2		2, 14, 1			1	23	6	3
8	30	35	3	6	75	77	2	0	91	91	1		3, 0, 1		
9	32	33	3	7	47	45	2	1	81	79	1	1	613	656	1
	2, 4, 1			8	24	14	3	2	53	54	2	2	31	34	1
0	302	313	1		2, 9, 1			3	110	111	2	3	242	254	1
1	234	242	1	0	76	75	1	4	63	62	2	4	192	197	1
2	316	319	1	1	8	11	5*	5	57	65	2	5	63	69	1
3	144	140	1	2	219	218	1	6	33	33	2	6	66	69	2
4	155	163	1	3	51	50	1	7	27	21	2	7	12	26	7*
5	119	123	1	4	77	81	1		2, 15, 1			8	9	5	8*
6	79	80	2	5	71	73	2	0	39	36	2	9	27	14	3
7	23	34	4	6	118	123	2	1	59	57	2		3, 1, 1		
8	32	30	2	7	32	41	2	2	29	22	2	0	411	431	1
9	34	31	2	8	35	28	2	3	49	45	2	1	152	161	1
	2, 5, 1				2, 10, 1			4	25	17	3	2	146	148	1
0	64	65	1	0	141	147	1	5	68	70	2	3	176	173	1
1	402	405	1	1	275	268	1	6	16	15	4	4	7	11	7*
2	250	244	1	2	135	136	1		2, 16, 1			5	99	102	1
3	286	285	1	3	32	28	2	0	91	90	2	6	32	32	2
4	42	45	2	4	39	41	2	1	92	92	2	7	86	93	2
5	218	222	1	5	36	38	3	2	29	28	3	8	27	25	3
6	141	146	1	6	14	28	6*	3	50	47	2	9	15	11	5*
7	106	107	2	7	40	46	2	4	28	30	3		3, 2, 1		
8	16	17	6*	8	9	13	8*	5	5	8	14*	0	228	247	1
9	25	12	3		2, 11, 1			6	27	23	2	1	77	73	1
	2, 6, 1			0	42	43	1		2, 17, 1			2	210	215	1
0	157	152	1	1	152	146	1	0	72	69	2	3	275	285	1
1	431	438	1	2	138	126	1	1	67	64	2	4	237	229	1
2	178	168	1	3	35	28	2	2	70	79	2	5	140	139	1
3	169	165	1	4	46	45	2	3	34	36	2	6	44	43	2
4	154	153	1	5	50	48	2	4	15	18	4*	7	20	25	4
5	91	86	1	6	114	105	2	5	44	45	2	8	18	10	3
6	148	149	1	7	59	64	2		2, 18, 1			9	4	11	22*
7	96	101	2	8	17	3	3	0	49	50	2		3, 3, 1		
8	13	16	7*		2, 12, 1			1	72	70	2	0	270	279	1
9	6	14	10*	0	32	31	2	2	44	46	2	1	138	137	1
	2, 7, 1			1	27	31	2	3	17	21	4	2	139	139	1
0	74	70	1	2	188	186	1	4	41	39	2	3	80	83	1
1	39	36	1	3	110	114	1	5	16	22	4*	4	131	139	1
2	403	397	1	4	16	30	6*		2, 19, 1			5	123	124	1
3	346	353	1	5	82	87	2	0	62	57	2	6	65	56	2
4	145	155	1	6	38	42	2	1	54	55	2	7	35	39	3
5	134	135	1	7	33	25	2	2	43	44	2	8	5	18	16*
6	191	181	2		2, 13, 1			3	30	31	3	9	30	12	2
7	20	17	4	0	146	144	1	4	59	54	2		3, 4, 1		

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	3, 4, 1			0	196	183	1	5	25	32	3	9	32	14	2
0	533	556	1	1	23	17	2	6	51	51	2		4, 1, 1		
1	335	333	1	2	55	51	1		3, 15, 1			0	140	148	1
2	308	312	1	3	141	136	1	0	78	77	2	1	204	204	1
3	165	169	1	4	27	25	2	1	86	89	2	2	83	79	1
4	153	152	1	5	194	196	1	2	79	81	2	3	151	158	1
5	121	126	1	6	50	57	2	3	26	25	3	4	40	33	1
6	89	92	2	7	17	16	4	4	35	29	2	5	15	28	4*
7	70	73	2	8	28	22	3	5	26	16	3	6	46	50	2
8	59	65	2		3, 10, 1			6	4	8	15*	7	80	81	2
9	25	8	2	0	61	60	1		3, 16, 1			8	23	17	4
	3, 5, 1			1	115	119	1	0	200	209	1	9	24	4	2
0	398	413	1	2	172	171	1	1	31	18	2		4, 2, 1		
1	165	169	1	3	76	77	1	2	36	37	2	0	119	117	1
2	445	451	1	4	134	134	1	3	58	58	2	1	272	279	1
3	278	288	1	5	34	40	3	4	58	60	2	2	133	132	1
4	176	169	1	6	46	45	2	5	27	18	2	3	286	286	1
5	93	91	1	7	23	37	3	6	23	26	3	4	74	71	1
6	84	87	2	8	4	16	15*		3, 17, 1			5	144	138	1
7	106	105	1		3, 11, 1			0	5	11	11*	6	43	43	2
8	35	34	3	0	75	74	1	1	60	68	2	7	19	25	4
	3, 6, 1			1	60	57	1	2	38	41	3	8	32	27	3
0	249	254	1	2	79	76	1	3	36	35	2	9	4	17	18*
1	232	237	1	3	53	59	2	4	54	53	2		4, 3, 1		
2	345	338	1	4	60	60	2	5	22	22	3	0	241	247	1
3	195	189	1	5	60	70	2		3, 18, 1			1	367	372	1
4	59	59	2	6	39	40	3	0	27	26	3	2	87	88	1
5	21	18	3	7	40	30	2	1	112	113	2	3	153	151	1
6	145	150	2		3, 12, 1			2	59	65	2	4	162	163	1
7	20	9	4	0	142	141	1	3	52	49	2	5	118	124	1
8	16	7	4	1	112	117	1	4	39	41	2	6	101	104	2
	3, 7, 1			2	76	76	1		3, 19, 1			7	88	85	2
0	226	218	1	3	67	67	2	0	49	48	2	8	44	42	2
1	23	9	2	4	73	66	2	1	30	28	2		4, 4, 1		
2	245	241	1	5	21	27	4	2	24	21	3	0	351	347	1
3	150	143	1	6	35	41	3	3	26	21	3	1	523	528	1
4	28	23	2	7	36	42	2		3, 20, 1			2	355	347	1
5	129	129	1		3, 13, 1			0	6	11	9*	3	76	75	1
6	110	102	2	0	131	130	1	1	26	27	2	4	151	147	1
7	36	29	2	1	57	57	2	2	22	18	3	5	79	81	1
8	16	9	4	2	161	161	1		3, 21, 1			6	114	120	2
	3, 8, 1			3	156	157	1	0	24	24	3	7	85	87	2
0	141	137	1	4	47	42	2		4, 0, 1			8	5	13	16*
1	197	199	1	5	48	50	2	0	157	159	1		4, 5, 1		
2	135	139	1	6	60	65	2	1	59	56	1	0	508	506	1
3	195	186	1	7	23	15	3	2	59	57	1	1	304	291	1
4	122	122	1		3, 14, 1			3	3	7	12*	2	212	209	1
5	138	145	1	0	82	85	2	4	89	86	1	3	145	146	1
6	82	77	2	1	146	143	1	5	55	49	2	4	177	179	1
7	27	16	3	2	182	183	1	6	35	33	2	5	26	29	3
8	26	9	3	3	56	55	2	7	37	35	2	6	186	182	2
	3, 9, 1			4	48	40	2	8	42	50	3	7	87	92	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	4, 5, 1			0	231	229	1	2	93	95	2	3	141	136	1
8	28	24	2	1	57	55	1	3	32	31	2	4	31	42	2
	4, 6, 1			2	149	143	1	4	12	17	5*	5	36	26	2
0	53	55	1	3	19	18	4	5	18	15	4	6	61	65	2
1	352	349	1	4	149	157	1		4, 18, 1			7	18	24	4
2	143	138	1	5	96	96	2	0	57	61	2	8	22	8	3
3	135	135	1	6	5	14	15*	1	14	6	5*		5, 4, 1		
4	187	185	1	7	26	30	3	2	29	23	3	0	414	436	1
5	127	135	1		4, 12, 1			3	39	35	2	1	132	134	1
6	33	36	3	0	111	110	1	4	33	33	3	2	220	219	1
7	40	36	2	1	111	109	1		4, 19, 1			3	186	190	1
8	17	7	4	2	189	193	1	0	38	47	2	4	52	55	2
	4, 7, 1			3	127	127	1	1	24	15	2	5	31	36	2
0	50	49	1	4	33	35	3	2	55	53	2	6	51	51	2
1	62	60	1	5	82	79	2	3	4	7	14*	7	36	37	2
2	46	49	1	6	47	53	2		4, 20, 1			8	38	36	2
3	68	73	1	7	33	27	2	0	4	12	14*		5, 5, 1		
4	156	150	1		4, 13, 1			1	4	13	17*	0	7	21	6*
5	42	35	2	0	199	202	1	2	15	12	4	1	297	296	1
6	67	72	2	1	130	131	1		5, 0, 1			2	89	87	1
7	45	51	2	2	109	107	1	1	131	136	1	3	121	121	1
8	19	11	3	3	108	109	2	2	40	42	1	4	71	71	1
	4, 8, 1			4	17	24	5*	3	94	96	1	5	32	28	3
0	20	13	2	5	27	25	3	4	21	38	3	6	33	25	2
1	161	162	1	6	61	58	2	5	63	66	2	7	53	59	2
2	138	146	1	7	18	22	3	6	15	0	4*	8	47	43	2
3	97	94	1		4, 14, 1			7	27	32	4		5, 6, 1		
4	32	26	2	0	149	149	1	8	32	37	3	0	617	625	1
5	107	111	1	1	33	31	2		5, 1, 1			1	235	231	1
6	76	75	2	2	37	34	2	0	115	111	1	2	115	111	1
7	69	66	2	3	103	104	2	1	292	295	1	3	136	141	1
8	20	8	3	4	51	52	2	2	127	126	1	4	15	23	4*
	4, 9, 1			5	41	47	2	3	93	95	1	5	86	87	2
0	22	24	2	6	34	32	2	4	140	142	1	6	42	35	2
1	101	103	1		4, 15, 1			5	81	79	1	7	31	33	3
2	94	99	1	0	81	83	2	6	34	33	2	8	21	27	4
3	47	39	2	1	5	10	17*	7	42	42	2		5, 7, 1		
4	78	79	1	2	77	80	2	8	26	12	3	0	267	261	1
5	71	74	2	3	15	16	5*		5, 2, 1			1	263	261	1
6	118	113	2	4	25	18	3	0	92	97	1	2	212	201	1
7	47	44	2	5	20	18	3	1	204	196	1	3	147	147	1
8	4	17	20*	6	23	19	3	2	236	237	1	4	91	93	1
	4, 10, 1				4, 16, 1			3	119	119	1	5	186	181	1
0	101	101	1	0	105	106	2	4	91	96	1	6	103	100	2
1	118	120	1	1	49	42	2	5	50	46	2	7	25	25	3
2	63	62	1	2	72	73	2	6	14	24	4*	8	28	23	3
3	155	157	1	3	26	28	3	7	30	26	3		5, 8, 1		
4	114	117	1	4	68	67	2	8	26	22	4	0	4	16	14*
5	124	119	2	5	32	31	2		5, 3, 1			1	151	146	1
6	85	90	2		4, 17, 1			0	70	70	1	2	107	102	1
7	21	20	4	0	26	23	3	1	233	227	1	3	151	154	1
	4, 11, 1			1	100	102	2	2	159	156	1	4	111	117	1

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	5, 8, 1			2	122	126	2	5	21	21	3	7	45	50	2
5	26	19	3	3	17	4	4	6	61	68	2	8	14	11	5*
6	86	82	2	4	62	64	2	7	55	59	2		6, 7, 1		
7	22	26	4	5	30	30	2	8	25	20	3	0	236	233	1
8	24	25	4	6	11	15	6*		6, 2, 1			1	78	73	1
	5, 9, 1				5, 15, 1			0	225	234	1	2	42	39	2
0	53	60	1	0	24	16	3	1	172	175	1	3	79	79	1
1	90	90	1	1	202	211	1	2	134	132	1	4	118	116	1
2	55	57	1	2	62	70	2	3	114	113	1	5	65	72	2
3	87	83	1	3	54	60	2	4	52	49	2	6	60	65	2
4	50	44	2	4	76	80	2	5	34	33	2	7	42	38	3
5	37	48	2	5	18	26	4	6	64	66	2		6, 8, 1		
6	50	48	2		5, 16, 1			7	52	51	2	0	71	69	1
7	37	34	3	0	29	30	3	8	22	17	4	1	122	120	1
	5, 10, 1			1	16	15	5*		6, 3, 1			2	70	71	1
0	57	61	2	2	56	57	2	0	152	152	1	3	138	138	1
1	62	62	1	3	71	78	2	1	75	73	1	4	157	161	1
2	81	82	1	4	19	21	4	2	252	252	1	5	31	25	2
3	70	68	2	5	12	26	7*	3	110	103	1	6	36	34	2
4	65	68	2		5, 17, 1			4	104	100	1	7	5	13	16*
5	5	19	16*	0	67	68	2	5	54	55	2		6, 9, 1		
6	33	33	3	1	56	54	2	6	76	76	2	0	182	177	1
7	46	45	2	2	39	40	2	7	31	41	3	1	42	42	2
	5, 11, 1			3	30	35	3	8	40	36	2	2	19	19	3
0	20	12	3	4	11	15	6*		6, 4, 1			3	30	24	2
1	192	189	1		5, 18, 1			0	452	439	1	4	99	90	2
2	47	51	2	0	14	3	4*	1	110	110	1	5	111	103	2
3	83	81	2	1	21	25	3	2	128	119	1	6	52	46	2
4	101	99	2	2	11	7	6*	3	114	110	1	7	7	13	11*
5	40	35	2	3	17	11	4	4	35	36	2		6, 10, 1		
6	70	71	2		5, 19, 1			5	40	39	2	0	4	1	11*
7	8	22	9*	0	4	15	15*	6	5	5	15*	1	59	55	2
	5, 12, 1			1	29	29	2	7	35	40	2	2	102	110	1
0	149	147	1	2	17	16	3	8	4	16	17*	3	40	40	2
1	98	95	1		5, 20, 1				6, 5, 1			4	118	119	2
2	40	38	2	0	34	28	2	0	243	238	1	5	65	59	2
3	91	94	2		6, 0, 1			1	368	361	1	6	78	77	2
4	31	32	3	0	52	52	2	2	125	116	1	7	33	34	2
5	35	36	3	1	168	177	1	3	72	77	1		6, 11, 1		
6	32	37	3	2	10	7	4*	4	95	94	1	0	167	170	1
7	28	21	2	3	198	199	1	5	71	72	2	1	72	76	2
	5, 13, 1			4	49	43	2	6	41	39	3	2	84	88	2
0	237	238	1	5	69	68	2	7	21	19	3	3	60	56	2
1	64	63	2	6	54	53	2	8	14	12	6*	4	125	131	2
2	69	66	2	7	51	45	2		6, 6, 1			5	81	84	2
3	80	80	2	8	18	15	3	0	236	232	1	6	22	17	3
4	85	86	2		6, 1, 1			1	48	44	1	7	13	4	4*
5	20	17	3	0	26	30	2	2	56	55	1		6, 12, 1		
6	29	27	2	1	140	132	1	3	34	37	2	0	180	179	1
	5, 14, 1			2	56	58	1	4	127	123	1	1	89	88	2
0	155	159	2	3	44	46	2	5	178	180	1	2	110	114	2
1	157	158	1	4	71	70	1	6	52	48	2	3	44	47	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	6, 12, 1			6	16	17	4	0	109	104	1	0	75	73	2
4	42	37	2	7	41	38	2	1	58	54	1	1	101	100	2
5	42	42	2	8	21	18	3	2	39	34	2	2	49	47	2
6	14	10	4*		7, 1, 1			3	50	46	2	3	13	11	5*
	6, 13, 1			0	39	39	1	4	54	60	2	4	59	58	2
0	101	102	2	1	95	88	1	5	38	39	2	5	30	39	3
1	134	131	1	2	132	135	1	6	26	22	3	6	38	37	2
2	57	57	2	3	70	67	1	7	48	45	2		7, 13, 1		
3	62	63	2	4	22	18	3		7, 7, 1			0	74	81	2
4	46	49	2	5	90	93	2	0	72	75	1	1	75	75	2
5	14	9	5*	6	85	88	2	1	159	158	1	2	112	118	2
6	25	23	3	7	25	30	3	2	76	76	1	3	36	37	2
	6, 14, 1			8	9	12	8*	3	63	69	2	4	42	43	2
0	18	9	4		7, 2, 1			4	87	79	2	5	44	49	2
1	105	102	2	0	20	14	2	5	22	19	4		7, 14, 1		
2	99	100	2	1	58	55	1	6	33	41	3	0	106	108	2
3	76	81	2	2	27	34	2	7	29	26	3	1	100	99	2
4	25	26	3	3	45	35	2		7, 8, 1			2	48	43	2
5	17	6	3	4	47	51	2	0	61	58	1	3	18	14	4
	6, 15, 1			5	32	45	3	1	65	58	1	4	25	36	4
0	28	33	3	6	99	94	2	2	43	41	2	5	4	20	14*
1	70	73	2	7	23	17	3	3	116	123	1		7, 15, 1		
2	100	105	2	8	21	12	3	4	84	83	2	0	16	9	4
3	22	33	4		7, 3, 1			5	73	64	2	1	35	41	2
4	7	12	10*	0	314	312	1	6	35	40	3	2	31	29	3
5	21	13	3	1	145	140	1	7	30	25	2	3	16	21	4*
	6, 16, 1			2	40	43	2		7, 9, 1			4	59	57	2
0	130	130	2	3	70	68	1	0	105	108	1		7, 16, 1		
1	47	45	2	4	64	69	2	1	55	57	2	0	28	18	3
2	39	36	2	5	17	14	4	2	25	25	3	1	30	29	3
3	54	53	2	6	16	18	5*	3	92	97	2	2	34	36	3
4	4	7	14*	7	13	16	6*	4	88	84	2	3	14	19	5*
	6, 17, 1			8	12	7	6*	5	116	120	2	4	13	20	5*
0	44	38	2		7, 4, 1			6	42	50	2		7, 17, 1		
1	30	24	2	0	143	144	1	7	16	2	4	0	40	43	2
2	26	26	3	1	97	96	1		7, 10, 1			1	25	30	3
3	19	15	3	2	121	120	1	0	120	121	1	2	24	23	3
4	12	27	6*	3	30	45	2	1	81	80	1	3	34	34	2
	6, 18, 1			4	49	52	2	2	65	68	2		7, 18, 1		
0	92	89	2	5	95	99	2	3	56	64	2	0	26	34	2
1	22	21	3	6	45	44	2	4	121	126	2	1	18	11	3
2	49	49	2	7	52	52	2	5	30	29	3	2	25	25	2
3	20	19	3		7, 5, 1			6	41	32	2		8, 0, 1		
	6, 19, 1			0	11	7	4*		7, 11, 1			0	61	53	2
0	38	37	2	1	111	117	1	0	135	143	1	1	21	2	2
1	6	2	10*	2	66	66	1	1	56	59	2	2	9	9	6*
	7, 0, 1			3	58	55	2	2	72	74	2	3	152	155	1
1	138	133	1	4	63	66	2	3	27	28	3	4	15	7	4
2	167	162	1	5	60	64	2	4	23	27	3	5	32	20	2
3	55	52	1	6	37	38	3	5	46	40	2	6	121	122	2
4	30	32	2	7	29	20	3	6	19	6	3	7	6	19	11*
5	50	45	2		7, 6, 1				7, 12, 1				8, 1, 1		

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	8, 1, 1			6	39	37	2	1	61	68	2	0	23	18	3
0	77	81	1	7	26	33	2	2	66	62	2	1	82	79	1
1	58	65	1		8, 7, 1			3	32	33	2	2	99	98	1
2	236	241	1	0	32	28	2	4	35	35	2	3	80	76	2
3	86	74	1	1	77	74	2	5	42	35	2	4	25	20	2
4	35	37	2	2	115	117	1		8, 14, 1			5	39	40	2
5	36	30	2	3	26	22	2	0	15	11	4*	6	41	41	2
6	50	44	2	4	129	129	2	1	19	17	4	7	16	25	4*
7	5	24	23*	5	99	94	2	2	38	36	2		9, 4, 1		
	8, 2, 1			6	5	16	16*	3	44	49	2	0	42	47	2
0	37	40	2	7	16	20	4*	4	35	39	2	1	34	43	3
1	142	144	1		8, 8, 1				8, 15, 1			2	21	6	3
2	105	108	1	0	10	17	5*	0	97	96	2	3	32	34	3
3	44	44	2	1	49	44	2	1	29	29	3	4	51	49	2
4	71	68	2	2	43	38	2	2	5	6	15*	5	33	33	3
5	30	42	3	3	31	29	3	3	28	27	2	6	29	24	3
6	27	25	3	4	127	135	2	4	13	4	5*		9, 5, 1		
7	45	47	2	5	40	40	2		8, 16, 1			0	15	10	4
	8, 3, 1			6	50	43	2	0	54	54	2	1	31	27	2
0	44	47	2		8, 9, 1			1	27	24	2	2	25	16	3
1	69	70	1	0	29	44	3	2	17	9	3	3	21	26	4
2	66	62	1	1	46	44	2	3	23	24	3	4	64	68	2
3	55	54	2	2	30	28	3		8, 17, 1			5	53	58	2
4	76	76	2	3	47	45	2	0	14	5	3	6	11	12	6*
5	74	74	2	4	39	35	3	1	31	31	2		9, 6, 1		
6	22	18	3	5	101	103	2		9, 0, 1			0	13	19	6*
7	23	18	3	6	27	26	2	1	192	194	1	1	26	17	2
	8, 4, 1				8, 10, 1			2	50	43	2	2	32	21	2
0	102	99	1	0	105	106	1	3	47	53	2	3	38	39	2
1	22	16	2	1	33	31	2	4	24	27	4	4	26	24	3
2	95	99	1	2	39	37	2	5	20	23	4	5	38	42	2
3	48	50	2	3	53	53	2	6	52	47	2	6	44	44	2
4	51	49	2	4	37	29	2	7	4	5	13*		9, 7, 1		
5	60	56	2	5	26	19	3		9, 1, 1			0	7	15	9*
6	45	49	2	6	54	62	2	0	17	12	3	1	63	67	2
7	14	3	4*		8, 11, 1			1	67	70	2	2	33	30	2
	8, 5, 1			0	27	24	3	2	136	138	1	3	5	18	13*
0	18	12	3	1	72	72	2	3	47	45	2	4	23	13	3
1	113	108	1	2	62	56	2	4	33	20	2	5	16	17	4*
2	36	34	2	3	47	40	2	5	37	41	2	6	27	27	2
3	92	93	1	4	42	36	2	6	45	44	2		9, 8, 1		
4	72	70	2	5	68	61	2	7	49	55	2	0	113	112	2
5	16	2	5*	6	38	35	2		9, 2, 1			1	46	57	2
6	43	57	3		8, 12, 1			0	37	29	2	2	56	53	2
7	17	9	4	0	19	16	3	1	129	132	1	3	48	56	2
	8, 6, 1			1	107	109	2	2	102	103	1	4	26	21	2
0	112	113	1	2	56	54	2	3	21	26	4	5	39	40	2
1	79	74	1	3	17	32	5*	4	28	25	2	6	4	3	14*
2	104	105	1	4	11	16	6*	5	63	58	2		9, 9, 1		
3	20	11	3	5	23	22	3	6	54	57	2	0	80	87	2
4	92	98	2		8, 13, 1			7	23	13	2	1	15	13	4*
5	62	64	2	0	79	74	2		9, 3, 1			2	39	36	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFc	Fc	Sig
9, 9, 1				1	54	55	2	10, 8, 1				5	4	11	14*
3	51	46	2	2	124	129	2	0	64	64	2	11, 2, 1			
4	59	62	2	3	43	41	2	1	29	27	3	0	77	76	2
5	36	30	2	4	30	28	3	2	64	68	2	1	26	15	3
9, 10, 1				5	26	29	3	3	5	13	16*	2	68	68	2
0	61	63	2	6	28	32	3	4	38	35	2	3	14	16	6*
1	57	61	2	10, 2, 1				5	48	46	2	4	15	6	4*
2	68	69	2	0	94	91	2	10, 9, 1				5	16	22	4
3	41	38	2	1	70	74	2	0	52	54	2	11, 3, 1			
4	8	18	10*	2	58	55	2	1	58	62	2	0	68	65	2
5	57	61	2	3	40	43	2	2	26	31	3	1	74	74	2
9, 11, 1				4	23	23	3	3	39	43	2	2	23	27	4
0	14	13	4*	5	5	10	15*	4	16	9	4	3	47	40	2
1	78	76	2	6	21	22	3	5	4	4	15*	4	38	37	2
2	58	66	2	10, 3, 1				10, 10, 1				5	18	9	4
3	43	34	2	0	22	17	3	0	33	37	2	11, 4, 1			
4	36	36	2	1	21	6	3	1	34	32	2	0	30	21	2
5	23	21	3	2	65	66	2	2	26	26	3	1	53	45	2
9, 12, 1				3	70	73	2	3	30	31	2	2	16	19	4*
0	55	57	2	4	10	10	7*	4	45	43	2	3	35	28	2
1	29	27	2	5	19	18	3	10, 11, 1				4	42	42	2
2	19	17	3	6	36	35	2	0	54	52	2	5	12	20	6*
3	15	16	4*	10, 4, 1				1	38	34	2	11, 5, 1			
4	21	17	3	0	49	51	2	2	11	28	7*	0	5	20	15*
9, 13, 1				1	61	52	2	3	26	21	2	1	33	28	2
0	5	20	15*	2	95	102	2	4	27	25	2	2	44	42	2
1	5	13	14*	3	53	62	2	10, 12, 1				3	21	27	3
2	23	20	3	4	61	61	2	0	10	9	7*	4	47	45	2
3	21	10	2	5	11	10	6*	1	42	44	2	5	4	18	17*
4	22	20	2	6	17	20	4	2	10	7	5*	11, 6, 1			
9, 14, 1				10, 5, 1				3	21	18	3	0	66	66	2
0	20	8	3	0	5	8	15*	10, 13, 1				1	10	5	6*
1	34	27	2	1	61	65	2	0	34	34	2	2	7	7	10*
2	5	2	13*	2	36	39	2	1	34	39	2	3	30	25	2
3	11	12	6*	3	5	4	16*	2	4	7	14*	4	26	33	3
9, 15, 1				4	49	47	2	3	9	12	7*	5	23	19	3
0	35	34	2	5	21	25	4	10, 14, 1				11, 7, 1			
1	8	11	8*	6	11	19	6*	0	36	40	2	0	71	77	2
2	33	31	2	10, 6, 1				1	27	15	2	1	31	31	3
9, 16, 1				0	105	104	2	2	4	7	12*	2	28	24	3
0	19	13	3	1	23	15	3	11, 0, 1				3	29	22	2
1	12	5	5*	2	32	28	2	1	69	78	2	4	23	17	3
10, 0, 1				3	78	77	2	2	38	34	2	11, 8, 1			
0	153	150	2	4	46	46	2	3	25	17	3	0	9	0	7*
1	134	142	2	5	36	40	2	4	17	5	3	1	47	49	2
2	83	91	2	10, 7, 1				5	35	33	2	2	18	9	3
3	47	51	2	0	77	78	2	11, 1, 1				3	34	41	2
4	5	12	15*	1	51	51	2	0	94	97	2	4	38	34	2
5	56	50	2	2	43	48	2	1	124	127	2	11, 9, 1			
6	20	27	4	3	34	39	2	2	105	98	2	0	44	38	2
10, 1, 1				4	48	46	2	3	27	16	2	1	63	61	2
0	119	125	2	5	8	5	9*	4	24	25	3	2	8	9	8*

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
11, 9, 1				4	16	9	3	0	23	19	2	-1	70	73	1
3	25	25	2	12, 6, 1				-1, -1, 1				-2	59	60	1
4	26	28	3	0	43	42	2	-1	494	524	1	-3	184	178	1
11, 10, 1				1	5	12	14*	-2	501	533	1	-4	105	108	1
0	38	52	2	2	38	42	2	-3	150	151	1	-5	64	64	2
1	25	23	3	3	9	7	7*	-4	243	243	1	-6	68	68	2
2	25	33	3	12, 7, 1				-5	57	55	1	-7	35	36	2
3	23	27	3	0	21	13	2	-6	29	23	2	-8	35	32	3
11, 11, 1				1	35	42	3	-7	62	57	2	-9	4	7	16*
0	16	11	4*	2	33	30	2	-8	73	74	1	-1, -7, 1			
1	21	18	3	3	21	19	3	-9	25	2	3	-1	159	161	1
2	24	27	3	12, 8, 1				-1, -2, 1				-2	230	224	1
3	24	8	3	0	41	43	2	-1	579	641	1	-3	249	247	1
11, 12, 1				1	35	38	2	-2	220	235	1	-4	153	148	1
0	30	30	2	2	23	25	3	-3	223	226	1	-5	120	120	1
1	24	9	2	3	17	11	4	-4	122	129	1	-6	67	59	2
2	7	6	9*	12, 9, 1				-5	75	79	1	-7	74	62	2
12, 0, 1				0	23	18	3	-6	68	66	2	-8	26	18	4
0	43	47	3	1	17	6	3	-7	43	36	2	-1, -8, 1			
1	20	31	4	2	4	13	13*	-8	49	48	2	-1	107	109	1
2	5	2	14*	12, 10, 1				-9	24	15	3	-2	82	84	1
3	33	38	2	0	38	36	2	-1, -3, 1				-3	156	144	1
4	20	15	3	1	21	14	3	-1	221	229	1	-4	83	87	1
12, 1, 1				13, 0, 1				-2	607	645	1	-5	32	32	2
0	38	44	2	1	12	7	5*	-3	173	179	1	-6	100	111	2
1	31	34	3	2	32	33	2	-4	387	394	1	-7	23	29	3
2	21	15	3	3	14	16	5*	-5	61	59	1	-8	24	16	3
3	13	10	5*	13, 1, 1				-6	55	58	2	-1, -9, 1			
4	18	19	4	0	36	34	2	-7	50	50	2	-1	315	306	1
12, 2, 1				1	4	10	16*	-8	18	17	4	-2	238	232	1
0	20	5	3	2	21	21	3	-9	22	23	4	-3	120	124	1
1	54	53	2	3	24	18	2	-1, -4, 1				-4	17	27	3
2	33	36	3	13, 2, 1				-1	936	1024	1	-5	28	27	2
3	33	38	3	0	48	58	2	-2	433	452	1	-6	81	74	2
4	39	38	2	1	20	17	3	-3	451	456	1	-7	40	40	2
12, 3, 1				2	17	11	3	-4	127	122	1	-8	8	14	10*
0	62	67	2	13, 3, 1				-5	88	89	1	-1,-10, 1			
1	48	50	2	0	16	0	4*	-6	144	147	1	-1	171	160	1
2	65	62	2	1	32	25	2	-7	5	17	18*	-2	186	187	1
3	42	46	2	2	18	10	3	-8	24	23	3	-3	116	105	1
4	19	17	4	13, 4, 1				-9	15	7	5*	-4	81	80	1
12, 4, 1				0	30	25	2	-1, -5, 1				-5	51	55	2
0	12	12	6*	1	31	29	2	-1	264	263	1	-6	30	24	3
1	28	27	3	2	35	42	2	-2	188	192	1	-7	72	78	2
2	37	34	2	13, 5, 1				-3	168	169	1	-8	26	17	2
3	16	24	5*	0	4	17	15*	-4	175	179	1	-1,-11, 1			
4	48	45	2	1	30	31	2	-5	146	145	1	-1	144	140	1
12, 5, 1				2	36	25	2	-6	56	57	2	-2	74	73	1
0	63	62	2	13, 6, 1				-7	37	39	2	-3	88	91	1
1	38	37	2	0	4	15	17*	-8	30	29	3	-4	25	27	2
2	20	20	3	1	19	23	3	-9	42	31	2	-5	66	58	2
3	26	30	3	13, 7, 1				-1, -6, 1				-6	90	83	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-1,-11, 1			-5	40	42	2	-9	29	31	3	-4	45	41	2
-7	60	53	2		-1,-19, 1				-2, -5, 1			-5	43	38	2
-8	33	32	2	-1	88	92	2	-1	399	404	1	-6	24	28	3
	-1,-12, 1			-2	19	21	3	-2	250	244	1	-7	41	46	2
-1	93	89	1	-3	39	36	2	-3	289	285	1	-8	27	14	2
-2	130	123	1	-4	83	85	2	-4	40	45	2		-2,-11, 1		
-3	60	58	2		-1,-20, 1			-5	221	222	1	-1	148	145	1
-4	50	44	2	-1	32	28	2	-6	141	146	2	-2	138	127	1
-5	81	88	2	-2	33	34	2	-7	108	107	2	-3	39	28	2
-6	41	32	2	-3	83	83	2	-8	17	17	5*	-4	47	45	2
-7	49	49	2		-1,-21, 1			-9	4	12	18*	-5	50	48	2
	-1,-13, 1			-1	31	38	3		-2, -6, 1			-6	109	105	1
-1	99	96	1	-2	29	34	3	-1	429	437	1	-7	58	64	2
-2	13	10	4*		-2, -1, 1			-2	179	167	1	-8	4	3	16*
-3	89	95	2	-1	1027	1202	1	-3	171	165	1		-2,-12, 1		
-4	97	99	2	-2	682	727	1	-4	154	153	1	-1	30	31	2
-5	36	35	3	-3	157	158	1	-5	90	86	1	-2	187	186	1
-6	41	43	2	-4	32	27	2	-6	147	149	1	-3	112	114	1
-7	27	21	2	-5	59	63	1	-7	97	101	2	-4	28	31	2
	-1,-14, 1			-6	85	86	2	-8	5	16	19*	-5	84	87	2
-1	65	61	2	-7	72	75	2	-9	17	15	4	-6	34	42	3
-2	67	67	2	-8	43	44	2		-2, -7, 1			-7	26	25	3
-3	39	38	2	-9	15	14	6*	-1	36	36	2		-2,-13, 1		
-4	45	43	2		-2, -2, 1			-2	401	396	1	-1	49	48	2
-5	53	54	2	-1	931	1058	1	-3	344	353	1	-2	48	51	2
-6	26	21	3	-2	337	342	1	-4	146	155	1	-3	101	104	1
-7	26	21	2	-3	82	83	1	-5	135	136	1	-4	42	38	2
	-1,-15, 1			-4	341	345	1	-6	183	181	1	-5	81	80	2
-1	80	84	2	-5	178	179	1	-7	21	17	4	-6	33	37	3
-2	23	19	3	-6	106	100	2	-8	32	27	3	-7	30	21	2
-3	30	20	2	-7	39	38	3		-2, -8, 1				-2,-14, 1		
-4	22	9	3	-8	68	70	2	-1	225	216	1	-1	77	78	1
-5	40	33	2	-9	37	32	2	-2	351	337	1	-2	55	54	2
-6	38	29	2		-2, -3, 1			-3	127	127	1	-3	111	111	2
	-1,-16, 1			-1	288	296	1	-4	116	114	1	-4	62	62	2
-1	54	54	2	-2	404	402	1	-5	41	44	2	-5	66	65	2
-2	45	37	2	-3	222	228	1	-6	70	76	2	-6	32	33	3
-3	44	43	2	-4	389	395	1	-7	42	45	2	-7	20	21	3
-4	37	37	2	-5	165	162	1	-8	18	13	3		-2,-15, 1		
-5	36	38	2	-6	16	18	4		-2, -9, 1			-1	57	57	2
-6	13	15	5*	-7	24	19	3	-1	3	10	16*	-2	22	22	3
	-1,-17, 1			-8	35	34	2	-2	222	219	1	-3	46	46	2
-1	83	80	2	-9	30	33	4	-3	52	49	1	-4	21	17	4
-2	44	48	2		-2, -4, 1			-4	79	81	1	-5	67	70	2
-3	28	22	3	-1	235	243	1	-5	73	72	2	-6	21	16	3
-4	49	55	2	-2	319	318	1	-6	115	123	2		-2,-16, 1		
-5	22	20	3	-3	143	140	1	-7	38	40	3	-1	92	93	2
	-1,-18, 1			-4	154	163	1	-8	26	28	3	-2	33	27	2
-1	59	59	2	-5	119	123	1		-2,-10, 1			-3	45	46	2
-2	58	54	2	-6	78	80	2	-1	275	267	1	-4	23	30	3
-3	46	47	2	-7	23	34	4	-2	138	136	1	-5	14	8	4*
-4	23	10	3	-8	31	30	3	-3	30	27	2	-6	28	23	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-2,-17, 1			-9	12	12	6*	-5	195	196	1	-1	17	18	4
-1	66	64	2		-3, -4, 1			-6	44	57	2	-2	36	37	2
-2	71	78	2	-1	333	333	1	-7	5	16	15*	-3	52	58	2
-3	33	35	2	-2	306	311	1	-8	29	22	3	-4	66	61	2
-4	23	19	3	-3	165	168	1		-3,-10, 1			-5	22	18	3
-5	42	44	2	-4	151	152	1	-1	112	118	1	-6	21	26	3
	-2,-18, 1			-5	122	126	1	-2	173	171	1		-3,-17, 1		
-1	74	70	2	-6	89	92	2	-3	78	77	1	-1	68	68	2
-2	49	47	2	-7	72	73	2	-4	132	134	1	-2	41	40	2
-3	9	21	9*	-8	70	65	2	-5	38	40	2	-3	42	35	2
-4	43	40	2	-9	24	9	3	-6	45	46	2	-4	52	53	2
-5	19	22	4		-3, -5, 1			-7	17	37	6*	-5	19	22	3
	-2,-19, 1			-1	167	170	1	-8	23	16	2		-3,-18, 1		
-1	50	56	2	-2	448	450	1		-3,-11, 1			-1	106	113	2
-2	45	44	2	-3	279	287	1	-1	56	57	1	-2	63	65	2
-3	34	31	2	-4	177	169	1	-2	72	75	1	-3	54	50	2
-4	56	54	2	-5	95	91	1	-3	52	60	2	-4	45	41	2
	-2,-20, 1			-6	85	87	2	-4	60	61	2		-3,-19, 1		
-1	70	80	2	-7	105	105	2	-5	66	70	2	-1	28	28	3
-2	30	27	2	-8	29	34	3	-6	42	40	2	-2	14	21	5*
-3	48	49	2		-3, -6, 1			-7	34	30	2	-3	30	22	2
	-2,-21, 1			-1	232	237	1		-3,-12, 1				-3,-20, 1		
-1	17	7	4	-2	344	337	1	-1	113	117	1	-1	28	27	2
	-3, -1, 1			-3	197	190	1	-2	79	77	1	-2	24	19	3
-1	154	162	1	-4	63	58	1	-3	68	68	2		-4, -1, 1		
-2	147	149	1	-5	26	18	2	-4	72	66	2	-1	202	203	1
-3	176	174	1	-6	143	150	2	-5	27	27	3	-2	84	79	1
-4	8	11	5*	-7	17	9	5*	-6	44	42	2	-3	151	158	1
-5	100	102	1	-8	5	7	21*	-7	36	42	3	-4	38	33	2
-6	36	32	2		-3, -7, 1				-3,-13, 1			-5	25	28	3
-7	87	93	2	-1	16	9	3	-1	58	56	2	-6	49	50	2
-8	22	25	3	-2	244	241	1	-2	162	162	1	-7	79	81	2
-9	11	11	7*	-3	151	142	1	-3	155	157	1	-8	5	18	16*
	-3, -2, 1			-4	19	24	3	-4	50	42	2	-9	4	4	17*
-1	79	75	1	-5	130	129	1	-5	54	50	2		-4, -2, 1		
-2	209	214	1	-6	112	103	2	-6	57	65	2	-1	273	280	1
-3	273	285	1	-7	31	29	3	-7	25	15	3	-2	131	132	1
-4	235	229	1	-8	22	9	4		-3,-14, 1			-3	284	286	1
-5	141	138	1		-3, -8, 1			-1	145	143	1	-4	68	71	1
-6	43	43	2	-1	199	200	1	-2	178	182	1	-5	145	138	1
-7	20	25	4	-2	135	138	1	-3	54	56	2	-6	39	42	2
-8	6	10	14*	-3	197	186	1	-4	44	40	2	-7	22	25	4
-9	5	11	19*	-4	120	122	1	-5	37	32	2	-8	24	26	3
	-3, -3, 1			-5	143	145	1	-6	51	51	2	-9	16	17	4*
-1	139	136	1	-6	83	77	2		-3,-15, 1				-4, -3, 1		
-2	140	140	1	-7	21	16	4	-1	88	88	2	-1	367	372	1
-3	82	84	1	-8	29	9	2	-2	71	81	2	-2	90	89	1
-4	133	139	1		-3, -9, 1			-3	32	25	2	-3	153	151	1
-5	119	124	1	-1	21	16	2	-4	30	30	2	-4	161	163	1
-6	62	56	2	-2	53	50	1	-5	30	16	2	-5	124	124	1
-7	34	39	3	-3	139	136	1	-6	18	8	3	-6	101	104	2
-8	10	17	7*	-4	19	25	4		-3,-16, 1			-7	86	84	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-4, -3, 1			-5	69	74	2	-2	79	73	2	-3	185	190	1
-8	33	42	4	-6	113	113	1	-3	20	28	4	-4	55	56	2
	-4, -4, 1			-7	47	44	2	-4	66	66	2	-5	27	35	3
-1	527	528	1	-8	26	17	3	-5	28	32	2	-6	52	50	2
-2	350	347	1		-4,-10, 1				-4,-17, 1			-7	35	37	3
-3	75	73	1	-1	116	120	1	-1	96	102	2	-8	33	35	3
-4	150	146	1	-2	63	61	1	-2	95	95	2		-5, -5, 1		
-5	76	81	2	-3	151	157	1	-3	27	31	3	-1	300	296	1
-6	113	120	2	-4	117	117	1	-4	17	17	4	-2	89	87	1
-7	78	87	2	-5	120	118	2	-5	19	16	3	-3	120	121	1
-8	27	13	3	-6	82	90	2		-4,-18, 1			-4	73	71	1
	-4, -5, 1			-7	24	20	3	-1	5	6	13*	-5	37	27	2
-1	305	291	1		-4,-11, 1			-2	34	23	2	-6	33	25	2
-2	213	208	1	-1	57	54	1	-3	32	34	3	-7	45	59	3
-3	147	145	1	-2	144	142	1	-4	31	33	2	-8	39	42	3
-4	174	178	1	-3	26	18	3		-4,-19, 1				-5, -6, 1		
-5	30	29	2	-4	150	157	1	-1	5	15	15*	-1	232	231	1
-6	179	182	2	-5	100	96	2	-2	54	54	2	-2	116	111	1
-7	87	92	2	-6	5	14	17*	-3	25	7	2	-3	141	141	1
-8	5	24	23*	-7	27	30	3		-4,-20, 1			-4	22	24	2
	-4, -6, 1				-4,-12, 1			-1	12	13	5*	-5	86	87	2
-1	354	349	1	-1	110	110	1	-2	13	12	4*	-6	38	35	2
-2	143	137	1	-2	187	193	1		-5, -1, 1			-7	30	33	3
-3	135	134	1	-3	127	128	1	-1	291	296	1	-8	33	27	2
-4	188	186	1	-4	36	34	2	-2	128	126	1		-5, -7, 1		
-5	128	135	1	-5	85	79	2	-3	90	95	1	-1	262	260	1
-6	35	36	2	-6	44	53	2	-4	142	141	1	-2	211	200	1
-7	41	36	2	-7	28	26	3	-5	84	80	1	-3	145	147	1
-8	19	7	5*		-4,-13, 1			-6	37	33	2	-4	89	93	1
	-4, -7, 1			-1	131	131	1	-7	30	42	3	-5	183	181	1
-1	65	61	1	-2	111	107	1	-8	17	12	5*	-6	105	100	2
-2	44	48	2	-3	108	109	2		-5, -2, 1			-7	25	25	3
-3	68	73	1	-4	25	24	3	-1	205	196	1	-8	31	23	3
-4	156	150	1	-5	25	25	3	-2	238	238	1		-5, -8, 1		
-5	41	35	2	-6	52	58	2	-3	120	119	1	-1	150	146	1
-6	72	72	2	-7	19	22	3	-4	87	97	1	-2	108	102	1
-7	49	51	2		-4,-14, 1			-5	52	46	2	-3	151	154	1
-8	26	11	3	-1	24	30	3	-6	18	24	4	-4	109	117	1
	-4, -8, 1			-2	32	34	3	-7	27	26	3	-5	21	20	4
-1	162	161	1	-3	106	103	2	-8	31	21	3	-6	81	82	2
-2	139	145	1	-4	49	53	2		-5, -3, 1			-7	23	27	4
-3	95	94	1	-5	44	47	2	-1	231	227	1	-8	24	25	3
-4	30	25	2	-6	33	32	2	-2	157	155	1		-5, -9, 1		
-5	102	110	2		-4,-15, 1			-3	142	136	1	-1	84	90	1
-6	73	75	2	-1	26	10	2	-4	35	42	2	-2	52	57	2
-7	59	66	2	-2	79	81	2	-5	29	26	3	-3	84	83	1
-8	15	8	4*	-3	17	16	3	-6	62	65	2	-4	51	44	2
	-4, -9, 1			-4	18	18	4	-7	30	24	3	-5	40	48	2
-1	98	103	1	-5	18	18	3	-8	17	8	4*	-6	46	48	2
-2	93	99	1	-6	24	19	3		-5, -4, 1			-7	32	33	2
-3	47	39	2		-4,-16, 1			-1	131	135	1		-5,-10, 1		
-4	75	79	2	-1	51	42	2	-2	220	219	1	-1	60	62	1

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-5,-10, 1			-3	29	35	3	-7	9	19	9*	-1	91	88	2
-2	83	82	1	-4	12	15	5*	-8	4	12	13*	-2	113	113	2
-3	71	68	2		-5,-18, 1				-6, -6, 1			-3	49	47	2
-4	68	68	2	-1	27	25	3	-1	48	44	1	-4	40	37	2
-5	18	19	4*	-2	15	6	5*	-2	51	55	2	-5	40	42	2
-6	32	32	3	-3	22	11	3	-3	36	36	2	-6	14	10	5*
-7	47	44	2		-5,-19, 1			-4	127	124	1		-6,-13, 1		
	-5,-11, 1			-1	29	29	2	-5	174	180	2	-1	134	131	1
-1	194	189	1	-2	10	16	6*	-6	49	48	2	-2	59	57	2
-2	44	51	2		-6, -1, 1			-7	47	50	2	-3	58	63	2
-3	79	81	2	-1	140	132	1	-8	19	11	3	-4	46	49	2
-4	99	99	2	-2	56	58	1		-6, -7, 1			-5	5	9	18*
-5	34	34	3	-3	43	46	2	-1	79	73	1	-6	24	23	3
-6	68	71	2	-4	71	70	1	-2	48	40	1		-6,-14, 1		
-7	24	22	3	-5	25	21	2	-3	78	79	1	-1	107	102	2
	-5,-12, 1			-6	60	67	2	-4	117	115	1	-2	102	100	2
-1	99	95	1	-7	56	59	2	-5	66	72	2	-3	81	82	2
-2	42	38	2	-8	17	20	4*	-6	58	65	2	-4	29	26	3
-3	94	94	2		-6, -2, 1			-7	44	38	2	-5	5	6	14*
-4	29	32	3	-1	167	175	1		-6, -8, 1				-6,-15, 1		
-5	46	36	2	-2	133	133	1	-1	119	120	1	-1	68	73	2
-6	35	37	2	-3	115	113	1	-2	72	71	1	-2	104	105	2
-7	34	21	2	-4	49	49	2	-3	137	138	1	-3	12	33	8*
	-5,-13,			-5	36	33	2	-4	154	160	1	-4	13	12	5*
-1	63	[illegible]	2	-6	69	66	2	-5	23	24	4	-5	4	14	16*
-2	68	66	2	-7	49	51	2	-6	37	34	2		-6,-16, 1		
-3	78	80	2	-8	15	17	4*	-7	14	13	5*	-1	51	45	2
-4	82	87	2		-6, -3, 1				-6, -9, 1			-2	39	36	2
-5	12	17	6*	-1	76	73	1	-1	43	42	2	-3	53	53	2
-6	30	27	2	-2	251	251	1	-2	23	19	3	-4	16	7	4
	-5,-14, 1			-3	112	103	1	-3	30	24	2		-6,-17, 1		
-1	153	158	1	-4	103	100	1	-4	98	90	2	-1	28	23	3
-2	121	125	2	-5	55	55	2	-5	113	103	2	-2	21	26	4
-3	5	3	14*	-6	78	76	2	-6	46	46	2	-3	19	15	3
-4	63	64	2	-7	35	41	2	-7	24	13	3	-4	22	27	3
-5	26	30	3	-8	32	36	2		-6,-10, 1				-6,-18, 1		
-6	19	15	3		-6, -4, 1			-1	55	55	2	-1	26	21	3
	-5,-15, 1			-1	106	110	1	-2	102	110	1	-2	51	49	2
-1	202	210	2	-2	128	119	1	-3	38	39	2	-3	13	19	5*
-2	61	70	2	-3	116	110	1	-4	121	119	2		-6,-19, 1		
-3	56	60	2	-4	34	36	2	-5	60	58	2	-1	17	2	4
-4	75	80	2	-5	31	38	3	-6	78	77	2		-7, -1, 1		
-5	26	27	3	-6	15	5	5*	-7	33	34	2	-1	97	88	1
	-5,-16, 1			-7	38	40	2		-6,-11, 1			-2	129	135	1
-1	28	15	2	-8	20	16	3	-1	76	76	2	-3	65	67	1
-2	53	57	2		-6, -5, 1			-2	83	89	2	-4	5	17	15*
-3	78	78	2	-1	365	361	1	-3	59	56	2	-5	90	93	2
-4	29	21	3	-2	125	116	1	-4	121	131	2	-6	85	88	2
-5	20	26	3	-3	71	77	1	-5	74	85	2	-7	30	30	3
	-5,-17, 1			-4	91	93	1	-6	12	16	6*	-8	8	12	8*
-1	54	54	2	-5	70	72	2	-7	4	4	14*		-7, -2, 1		
-2	40	40	2	-6	37	40	2		-6,-12, 1			-1	57	55	1

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-7, -2, 1			-3	117	123	1	-1	26	29	3	-1	77	73	2
-2	28	34	2	-4	85	83	2	-2	38	36	2	-2	101	105	1
-3	47	35	1	-5	73	65	2	-3	19	19	3	-3	17	11	3
-4	43	52	2	-6	38	39	2	-4	22	20	3	-4	90	98	2
-5	38	45	2	-7	22	25	3		-7,-17, 1			-5	67	64	2
-6	99	94	2		-7, -9, 1			-1	34	29	2	-6	31	37	3
-7	17	17	4	-1	53	56	2	-2	29	23	2	-7	27	33	2
-8	9	12	8*	-2	20	26	4	-3	31	34	2		-8, -7, 1		
	-7, -3, 1			-3	91	97	2		-7,-18, 1			-1	78	74	1
-1	145	140	1	-4	87	84	2	-1	4	11	17*	-2	116	117	1
-2	42	43	2	-5	117	121	2	-2	22	25	3	-3	21	23	3
-3	71	67	1	-6	43	50	3		-8, -1, 1			-4	130	130	2
-4	62	69	2	-7	19	2	4	-1	55	65	2	-5	97	94	2
-5	17	14	4		-7,-10, 1			-2	237	241	1	-6	5	16	17*
-6	20	18	4	-1	78	80	2	-3	83	75	1	-7	18	19	3
-7	5	16	12*	-2	67	69	2	-4	37	37	2		-8, -8, 1		
-8	13	7	4*	-3	52	64	2	-5	30	31	3	-1	47	44	2
	-7, -4, 1			-4	118	126	2	-6	45	44	2	-2	42	39	2
-1	97	95	1	-5	29	29	3	-7	27	24	3	-3	30	29	3
-2	121	120	1	-6	41	32	2		-8, -2, 1			-4	128	135	2
-3	41	45	2		-7,-11, 1			-1	145	144	1	-5	43	40	2
-4	48	51	2	-1	50	59	2	-2	106	108	1	-6	51	43	2
-5	94	99	2	-2	76	73	2	-3	38	44	2		-8, -9, 1		
-6	40	44	2	-3	28	29	3	-4	69	68	2	-1	50	44	2
-7	52	52	2	-4	21	27	3	-5	32	42	3	-2	30	27	2
	-7, -5, 1			-5	42	40	2	-6	28	25	3	-3	47	45	2
-1	114	116	1	-6	12	6	6*	-7	48	47	2	-4	42	35	2
-2	68	66	1		-7,-12, 1				-8, -3, 1			-5	97	103	2
-3	56	55	2	-1	98	100	2	-1	65	69	2	-6	20	26	3
-4	68	66	2	-2	54	47	2	-2	60	62	2		-8,-10, 1		
-5	63	64	2	-3	15	11	4*	-3	58	54	2	-1	30	31	3
-6	47	38	2	-4	62	59	2	-4	77	76	2	-2	32	37	3
-7	25	21	3	-5	32	39	3	-5	74	74	2	-3	48	53	2
	-7, -6, 1			-6	34	36	2	-6	19	18	3	-4	37	29	2
-1	57	54	1		-7,-13, 1			-7	14	18	5*	-5	15	19	5*
-2	35	34	2	-1	73	75	2		-8, -4, 1			-6	57	62	2
-3	50	45	2	-2	114	118	2	-1	12	16	5*		-8,-11, 1		
-4	55	60	2	-3	37	38	2	-2	95	98	1	-1	71	71	2
-5	50	39	2	-4	37	43	3	-3	49	50	2	-2	60	55	2
-6	5	22	18*	-5	50	49	2	-4	50	49	2	-3	45	39	2
-7	48	45	2		-7,-14, 1			-5	61	56	2	-4	38	37	2
	-7, -7, 1			-1	103	99	2	-6	46	49	2	-5	67	61	2
-1	161	158	1	-2	40	43	2	-7	8	3	7*	-6	28	35	3
-2	75	76	2	-3	5	14	17*		-8, -5, 1				-8,-12, 1		
-3	63	68	2	-4	39	37	2	-1	112	108	1	-1	108	109	2
-4	84	79	2	-5	23	21	2	-2	36	34	2	-2	55	54	2
-5	5	20	15*		-7,-15, 1			-3	90	93	2	-3	37	32	2
-6	43	41	2	-1	38	41	2	-4	70	70	2	-4	16	16	4*
-7	30	26	2	-2	39	29	2	-5	5	1	18*	-5	21	22	3
	-7, -8, 1			-3	20	21	3	-6	47	57	2		-8,-13, 1		
-1	61	58	1	-4	58	57	2	-7	23	9	3	-1	65	69	2
-2	43	41	2		-7,-16, 1				-8, -6, 1			-2	64	62	2

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	-8,-13, 1			-1	24	27	3	-2	27	20	2	-5	40	40	2
-3	30	33	3	-2	19	16	4	-3	17	10	3		-10, -7, 1		
-4	43	35	2	-3	32	26	2	-4	17	21	4	-1	53	51	2
-5	41	36	2	-4	70	68	2		-9,-14, 1			-2	46	49	2
	-8,-14, 1			-5	55	59	2	-1	33	27	2	-3	32	39	2
-1	5	17	23*	-6	5	12	17*	-2	13	2	4*	-4	44	46	2
-2	33	37	3		-9, -6, 1			-3	23	12	2	-5	8	5	9*
-3	46	49	2	-1	7	17	9*		-9,-15, 1				-10, -8, 1		
-4	37	39	2	-2	30	21	2	-1	4	11	14*	-1	29	27	2
	-8,-15, 1			-3	43	39	2	-2	35	31	2	-2	65	68	2
-1	32	29	2	-4	22	24	3		-9,-16, 1			-3	10	13	6*
-2	15	6	4*	-5	35	42	2	-1	16	5	3	-4	37	36	2
-3	30	27	2	-6	45	44	2		-10, -1, 1			-5	49	46	2
-4	20	4	3		-9, -7, 1			-1	56	54	2		-10, -9, 1		
	-8,-16, 1			-1	64	67	2	-2	122	129	2	-1	55	62	2
-1	29	24	2	-2	31	30	3	-3	32	41	3	-2	25	30	4
-2	4	9	16*	-3	5	19	16*	-4	27	28	3	-3	40	43	2
-3	24	24	2	-4	25	13	3	-5	29	29	3	-4	16	9	4
	-8,-17, 1			-5	10	17	6*	-6	38	32	2	-5	14	4	3
-1	31	31	2	-6	25	27	3		-10, -2, 1				-10,-10, 1		
	-9, -1, 1				-9, -8, 1			-1	68	73	2	-1	38	32	2
-1	67	70	2	-1	54	58	2	-2	58	54	2	-2	24	26	3
-2	137	139	1	-2	60	53	2	-3	37	43	2	-3	33	32	2
-3	48	45	2	-3	52	56	2	-4	33	23	2	-4	43	43	2
-4	13	20	6*	-4	15	21	5*	-5	13	10	4*		-10,-11, 1		
-5	43	41	2	-5	44	40	2	-6	26	22	2	-1	33	34	2
-6	41	44	3	-6	20	4	4		-10, -3, 1			-2	11	28	9*
-7	54	55	2		-9, -9, 1			-1	5	7	16*	-3	28	21	2
	-9, -2, 1			-1	19	13	3	-2	64	66	2	-4	29	26	2
-1	132	132	1	-2	39	36	2	-3	75	73	2		-10,-12, 1		
-2	102	102	1	-3	45	46	2	-4	20	9	3	-1	37	44	2
-3	32	26	2	-4	62	63	2	-5	16	18	4	-2	5	7	13*
-4	19	24	4	-5	25	30	3	-6	34	36	3	-3	18	18	3
-5	55	58	2		-9,-10, 1				-10, -4, 1				-10,-13, 1		
-6	55	57	2	-1	54	61	2	-1	57	52	2	-1	40	39	2
-7	9	13	9*	-2	66	69	2	-2	96	102	2	-2	13	7	5*
	-9, -3, 1			-3	32	38	3	-3	58	61	2	-3	4	12	15*
-1	80	79	1	-4	22	18	3	-4	59	61	2		-10,-14, 1		
-2	94	97	1	-5	60	61	2	-5	20	10	3	-1	4	15	17*
-3	79	76	2		-9,-11, 1			-6	18	20	4	-2	16	7	4
-4	22	20	3	-1	79	76	2		-10, -5, 1				-11, -1, 1		
-5	38	40	2	-2	52	65	2	-1	62	65	2	-1	128	127	2
-6	37	41	2	-3	38	34	2	-2	40	39	2	-2	108	98	2
-7	25	25	2	-4	42	36	2	-3	12	4	5*	-3	28	16	3
	-9, -4, 1			-5	25	21	3	-4	41	47	2	-4	30	25	3
-1	37	43	2		-9,-12, 1			-5	29	25	3	-5	22	11	3
-2	17	6	3	-1	30	27	2	-6	17	19	3		-11, -2, 1		
-3	40	34	2	-2	26	17	2		-10, -6, 1			-1	17	15	4
-4	51	48	2	-3	18	16	3	-1	22	15	4	-2	64	68	2
-5	25	34	3	-4	4	17	17*	-2	32	28	2	-3	21	16	4
-6	31	24	2		-9,-13, 1			-3	72	77	2	-4	17	5	4
	-9, -5, 1			-1	12	13	6*	-4	39	46	2	-5	21	21	3

Columns are 10Fo 10Fc 10Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
-11, -3, 1				-4	21	17	3	-1	51	53	2	-12, -8, 1			
-1	77	73	2	-11, -8, 1				-2	37	36	2	-1	35	38	2
-2	30	27	2	-1	47	49	2	-3	36	38	2	-2	12	25	5*
-3	47	40	2	-2	23	9	3	-4	39	38	2	-3	22	11	2
-4	32	37	2	-3	43	41	2	-12, -3, 1				-12, -9, 1			
-5	20	9	3	-4	38	34	2	-1	43	50	2	-1	24	6	2
-11, -4, 1				-11, -9, 1				-2	67	62	2	-2	16	14	3
-1	47	45	2	-1	60	61	2	-3	39	46	2	-12,-10, 1			
-2	17	19	4	-2	12	10	6*	-4	26	16	3	-1	19	14	3
-3	38	28	2	-3	17	25	5*	-12, -4, 1				-13, -1, 1			
-4	38	42	2	-4	28	28	3	-1	24	27	4	-1	11	10	5*
-5	23	20	3	-11,-10, 1				-2	34	34	2	-2	17	21	3
-11, -5, 1				-1	23	23	3	-3	24	24	3	-3	19	18	3
-1	28	27	2	-2	31	33	2	-4	47	45	2	-13, -2, 1			
-2	44	42	2	-3	30	27	2	-12, -5, 1				-1	4	17	15*
-3	13	28	6*	-11,-11, 1				-1	38	36	2	-2	4	11	20*
-4	49	45	2	-1	24	18	3	-2	5	20	16*	-13, -3, 1			
-5	25	18	3	-2	23	27	3	-3	28	30	2	-1	27	25	3
-11, -6, 1				-3	4	8	16*	-4	11	9	5*	-2	15	10	5*
-1	14	5	5*	-11,-12, 1				-12, -6, 1				-13, -4, 1			
-2	14	7	4*	-1	13	9	4*	-1	15	12	4*	-1	39	29	2
-3	31	25	2	-2	7	6	8*	-2	45	41	2	-2	44	42	2
-4	35	34	2	-12, -1, 1				-3	24	7	3	-13, -5, 1			
-5	24	19	2	-1	39	34	2	-12, -7, 1				-1	28	31	3
-11, -7, 1				-2	5	15	19*	-1	47	42	2	-2	28	25	2
-1	32	31	2	-3	21	9	3	-2	23	30	3	-13, -6, 1			
-2	32	24	2	-4	17	19	4*	-3	17	18	4	-1	27	22	2
-3	27	23	2	-12, -2, 1											