CHAPTER-I

Preparation and utility of α-chlorosulfides in organic synthesis
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1. Introduction

Compounds with chlorine and sulfur atoms attached to the same carbon atom are known as α-chlorosulfides. A typical example is depicted below.

1

The first discovered α-chlorosulfide 3 was derived from dimethyl sulfide 2 in 18th century.\(^1\) Proper preparation and investigation of α-chlorosulfides were performed in 1949, Scheme 1. Although discovered many years back its application in organic synthesis was very limited.

Scheme 1.

2. Preparations of α-chlorosulfides

α-Chlorosulfides can be prepared from four different precursors, that include; 1. alkyl sulfides, 2. sulfoxides, 3. aldehydes and thiols and 4. α-diazocarbonyl compounds.

2.1. From alkyl sulfides

The most widely used route to prepare α-chlorosulfides is via direct chlorination of alkyl sulfides having at least one hydrogen atom at the α-position, Scheme 2.

Scheme 2.

Bohme et al.\(^2\) reported the preparation of mono chloro dialkyl sulfide by treating dialkyl sulfide with one equivalent of chlorine in carbon tetrachloride at -20 °C. But since chlorine is not a convenient reagent to handle it was replaced with more convenient chlorinating reagents such as sulfuryl chloride, thionyl chloride, N-chlorosuccinimide (NCS), N-chlorophthalimide,
trichloroisocyanuric acid (chloreal), iodobenzene dichloride and benzene sulphenyl chloride. Among these chlorinating agents, NCS is the most widely used reagent, the reason being that it is a solid, commercially available, inexpensive, easy to handle and can be stored at room temperature. Also by using NCS the extent of chlorination is easily limited to the mono chloride stage.

In general alkyl sulfides containing β-hydrogen atoms fails to give α-chlorosulfides cleanly with sulfuryl chloride and thionyl chloride, the reason being that α-chlorosulfides undergo dehydrochlorination via β-elimination to yield vinyl sulfides, as depicted in Scheme 3.

Scheme 3.

Later Wilson et al. found that addition of an equivalent of triethylamine or pyridine to the reaction mixture suppressed β-elimination to furnish α-chlorosulfides in good yield. The introduction of NCS in 1966 led to major improvements in the synthesis of α-chlorosulfides. It can be used for acid sensitive substrates too. NCS is soluble in carbon tetrachloride and other organic solvents at room temperature where as its conjugate product succinimide is not. Taking advantage of this, solutions of chlorosulfides are prepared in organic solvents, filtered and used without further purification. Other non-polar solvents that have been used with NCS include dichloromethane, chloroform and benzene. It cannot be prepared satisfactorily in water or hydroxylic solvents due to their high reactivity and susceptibility to undergo solvolysis. It is also evident that NCS is compatible with many functional groups such as alkene 10, ketone 12, cyanide 14, ester, ketal 16 and anhydride 18, in the course of sulfide chlorination, but allylic rearrangement is observed with allyl phenyl sulfide 20, Scheme 4.
Although NCS continues to be the most popular reagent for sulfide chlorination, a less expensive alternative was found several years later. In 1975 Cohen et al.\textsuperscript{5} reported that trichloroisocyanuric acid commercially known as chloreal 22 was a better chlorinating agent than NCS for $\alpha$-chlorination of allylic sulfides. For instance, phenyl crotyl sulfide 23 afforded the corresponding $\alpha$-chlorosulfide 24 in 36% yield using NCS after 24 h, while the yield was quantitative with chloreal, Scheme 5.

**2.1.1 Mechanism of sulfide chlorination by NCS**

Initially the sulfide I reacts with NCS II to afford S-chloro sulfonium ion III. This can further react by two different pathways, Scheme 6. In path A, the intermediate III forms
sulfonium ion IV, by loss of hydrogen in α-position and succinimide IX. Intermolecular capture of the chloride ion by the sulfonium ion V would deliver chlorosulfide VI. In path B, the intermediate III is converted to intermediate VII and consequent formation of succinimide IX. 1,2 Rearrangement of chlorine atom from sulfur to carbon would yield chlorosulfide VI.°

Scheme 6.

2.2. α-Chlorosulfides from sulfoxides

The formation of α-chlorosulfides was accomplished by the reaction of sulfoxides with thionyl chloride or an acid chloride. The reaction of methyl phenyl sulfoxide 25 with p-nitrobenzyol chloride or thionyl chloride in benzene solution gave chloromethyl phenyl sulfide 26, Scheme 7.

Scheme 7.

The reaction of phenyl methyl sulfoxide with thionyl chloride may involve the formation of sulfonium salt X, Scheme 8. The -OSOCI group may be displaced (liberating SO₂ and Cl⁻) by attack of chloride ion on sulfur to yield the product XI. The intermediate chlorosulfonium chloride XI also obtained from the chlorination of phenyl methyl sulfide probably decomposes to XII, which subsequently affords phenyl chloromethyl sulfide 26.

Preparing α-chlorosulfides from sulfoxide is synthetically not much useful because generally the sulfoxides are prepared from the corresponding sulfides and moreover the sulfide can directly be converted to α-chlorosulfides.
2.3. α-Chlorosulfides from aldehydes and thiols

Bohme et al. reported the condensation of aldehydes with thiols in the presence of anhydrous hydrogen chloride to yield α-chlorosulfides, Scheme 9. This synthesis is quite versatile; use of formaldehyde gave primary chloride, while higher aldehydes lead to secondary chlorides.

Scheme 8.

\[
\begin{align*}
\text{Ph-S-CH}_3 + \text{SOCl}_2 & \rightarrow \text{C}_6\text{H}_6 \rightarrow \left[ \text{Ph-S-CH}_3 \right]^{\ominus} \rightarrow \left[ \text{Ph-S-CH}_3 \right]^{\ominus} \\
\text{Cl} & \rightarrow \left[ \text{Ph-S-CH}_3 \right]^{\ominus} \rightarrow \left[ \text{Ph-S-CH}_3 \right]^{\ominus} \\
\text{HCl} & \rightarrow \left[ \text{Ph-S-CH}_3 \right]^{\ominus}
\end{align*}
\]

Scheme 9.

This process can be used to prepare regiochemically pure α-chlorosulfides whereas use of NCS with unsymmetrical dialkyl sulfides could reasonably be expected to be non-regioselective.

Scheme 10.
For example chlorination of benzyl p-methylbenzyl sulfide 32 using NCS gave both regioisomeric mono chlorosulfides 33 & 34 in almost equal ratio, whereas the condensation alternative with aldehyde, thiol and HCl gave one regioisomer exclusively, Scheme 10.9

2.4. α-Chlorosulfides from α-diazocarbonyl compounds

Bestmann et al.10 reported that α-diazocarbonyl compounds and benzene sulfenyl chloride 40 react together with the loss of nitrogen at room temperature to yield α-chloro-α-(phenylthio) carbonyl derivatives 41 and 43, Scheme 11. α-Diazoketones can be obtained in excellent yield from acyl chlorides and diazomethane.

Scheme 11.

Some enolizable β-diketones can be reacted directly with sulfenyl chloride to furnish α-chlorosulfides.11

Scheme 12.

3. Reaction of α-Chlorosulfides

α-Chlorosulfides exhibits a range of reactivity which make them useful intermediates in organic synthesis. Their ready oxidation to α-chlorosulfones with suitable oxidizing agent has been utilized extensively in the Ramberg-Backlund olefination. They can undergo solvolysis in aqueous media to serve as a source of aldehydes and ketones. α-Chlorosulfides can be reacted with Grignard reagents to form alkylated products. It is also an important source of reactive electrophiles in S_N2 reactions and alkylation reactions.
3.1. Ramberg-Backlund reaction

The Ramberg-Backlund reaction is the conversion of α-halo sulfone 47 into an alkene 50 in presence of a base with extrusion of sulfur dioxide, Scheme 13. The carbanion 48 formed by deprotonation gives an unstable thiirane dioxide 49 that decomposes with elimination of SO₂. This elimination step is considered to be a concerted cycloelimination. Compounds 51 and 54 provided the corresponding alkenes 53 and 56 in good yield.

Scheme 13.

3.2. Hydrolysis

The use of α-chlorosulfides as aldehyde and ketone equivalents is widespread. α-Chloromethyl alkyl sulfide 57 decomposes in water producing HCl, formaldehyde 28 and the corresponding dithioacetal 58. Sulfides 59 and 61 yield the aldehyde 60 and keto derivative 62 respectively.

Scheme 14.
3.3. Reactions with alcohols, carboxylic acids

The behavior of α-chlorosulfides in reaction with alcohols, carboxylic acids, thiols and amines is a convenient form of functional group protection. Corey and co-workers\textsuperscript{14} reported the methyl thiomethyl (MTM) hemithioacetal group using the commercially available chloromethyl methyl sulfide 3. Chloromethyl phenyl sulfide (PTM) is also used for the same purpose.

Scheme 15.

Carboxylic acids furnish MTM protected esters when treated with chloromethyl methyl sulfide. Intramolecular reaction between the chlorosulfide generated in situ with the carboxy group in \textsuperscript{64} furnished sulfonylated lactone \textsuperscript{65}, Scheme 16. Reaction of an alcohol in the presence of silver oxide with the α-chlorosulfide delivered α-alkoxylated sulfides, for instance, compound \textsuperscript{66} provided compound \textsuperscript{67}.

Scheme 16.

3.4. Reaction with carbon nucleophiles

Chloromethyl phenyl sulfide \textsuperscript{26} reacts with phenylmagnesium bromide \textsuperscript{68} to form the coupled product \textsuperscript{69}.\textsuperscript{15} This is a general method for introducing α-alkyl or aryl substituents, Scheme 17.

Scheme 17.

Chloromethyl phenyl sulfide and \textit{t}-butylmagnesium bromide did not yield the coupled product, rather the reagent acts as a reducing agent to furnish methyl phenyl sulfide. In general primary or secondary alkyl, aryl, vinyl and acetylenic Grignards on reaction with α-
chlorosulfides provides coupled product with moderate yields, Scheme 18. This approach nicely complements the alternative of dithiane lithiation followed by treatment with an electrophile, a process that is less effective with secondary halides and quite ineffective with vinyl and aryl systems.\textsuperscript{16,17} Due to reactive nature of chlorosulfides, reaction with Grignard reagents afforded products in poor yields. For example, chloro sulfide 70 delivered more than one product (72-76).

Scheme 18.

3.5. Regiospecific \(\alpha\)-methylenation and \(\alpha\)-methylation of ketones

\(\alpha\)-Chlorosulfides can be reacted with silylenol ethers to provide the coupled products. Ian Paterson and Ian Fleming\textsuperscript{18} reported regiospecific \(\alpha\)-methylenation and \(\alpha\)-methylation of ketones using chlorosulfide, Scheme 19. Silylenol ethers can be prepared in high yield from the corresponding ketones regiospecifically using appropriate conditions which upon treatment with chloromethyl phenyl sulfide 26 in the presence of Lewis acid like titanium tetrachloride underwent alkylation to provide \(\alpha\)- or \(\alpha'\) phenylthio methyl ketones. Oxidative sulfur removal of 85 then provides the \(\alpha\)-methylene ketones 87. Alternatively sulfur can be removed reductively by Raney Ni to provide \(\alpha\)- or \(\alpha'\) methylated ketones 86 and 90.
3.6. α-Chlorosulfides as reactive electrophiles in aromatic alkylation.

Friedel Craft’s alkylation of benzene 91 with chloromethyl phenyl sulfide 26 affords benzyl phenyl sulfide 92 in the presence of mild Lewis acid catalysts like stannic or zinc halides in excellent yield, Scheme 20. The reaction is well behaved under mild conditions owing to the high reactivity of these α-chlorosulfides which act as better electrophiles than simple alkyl halides.19

Scheme 20.

This method is useful for getting various aromatic aldehydes. For example alkylation of substituted benzene 93 with dichloromethyl methyl sulfide 94 as the electrophile in the presence of Lewis acid provides substituted benzaldehyde 96 after hydrolysis, Scheme 21. Alternatively this method can be used to synthesize polyalkylated phenols. For example, alkylation of a 2,6-disubstituted phenol 97 with chloromethyl phenyl sulfide 26 followed by Raney Nickel hydrogenolysis of the ensuing product 98 gives 2,4,6-trisubstituted phenol 99.20
Generally α-chlorocarbonyl compounds are inert towards Friedel-Crafts alkylation reaction, whereas α-chloro-α-(alkyl or arylthio)carbonyl compounds are good electrophiles towards Friedel-Crafts alkylation due to their high reactivity. Scheme 22.
4. Previous synthesis of chiral \( \alpha \)-substituted sulfides and its applications in organic synthesis

Only a couple of methods have been disclosed for the preparation of chiral \( \alpha \)-substituted sulfides. The first method involves preparing chiral \( \alpha \)-substituted sulfide from chiral pool starting materials and the second route exploits organocatalysis.

4.1. From chiral pool starting materials

4.1.1. Preparation of \( \alpha \)-branched \( N \)-tert-butyloxy carbonyl (Boc)-protected \( N \)-allylamines from substituted chiral allyl sulfide

Bach and co-workers\(^\text{22}\) reported Fe(II)-catalyzed imidation of allyl sulfides and subsequent [2,3]-sigmatropic rearrangement to furnish \( \alpha \)-branched \( N \)-tert-butyloxy carbonyl (Boc)-protected \( N \)-allylamines. Commercially available methyl lactate \( \text{107} \) has been utilized for the preparation of allyl sulfide \( \text{113} \), Scheme 23. Thus the hydroxy group of methyl lactate was converted to the corresponding tosylate. Nucleophilic substitution of the tosylate in \( \text{108} \) by thiophenolate delivered chiral methyl 2-phenyl sulfanyl propionate \( \text{109} \).

Scheme 23.

The ester \( \text{109} \) was converted to acrylate \( \text{110} \) by reduction to the aldehyde and subsequent Horner-Wadsworth-Emmons reaction. Reduction of the unsaturated ester \( \text{110} \) with DIBAL-H at 0 °C in \( \text{CH}_2\text{Cl}_2 \) furnished the allyl alcohol \( \text{111} \), whose enantiomeric purity was determined by derivatization with (-)-menthylchloroformate. GLC and \(^1\text{H} \) NMR analysis revealed the presence of a single diastereoisomer (>95% de). Subsequent transformations of hydroxyl to bromide followed by reduction with LAH furnished target sulfide \( \text{113} \). The \( \alpha \)-branched allyl sulfides \( \text{110} \)
and 113 were used as substrates for the Fe(II) catalyzed sulfilimine preparation and the subsequent rearrangement.

Attempted sulfimidation/rearrangement reaction of substrate 110 gave poor yield of the corresponding allylamine derivative 115. Notably the chirality transfer was poor, the enantiomeric excess of 115 was determined to be 39% by chiral HPLC. The low yield of the reaction 110→115 was explained as being due to the weak nucleophilicity of the sulfide and facile C-S bond cleavage which shuts down the catalytic cycle. Surprisingly, the recovered sulfide 110 & 113 had reduced optical purity (75% ee from 95% ee).

Scheme 24.

4.1.2. Sulfonium ylide formation-[2,3]-sigmatropic rearrangement of chiral allylic sulfides

The [2,3]-sigmatropic rearrangement of allylic sulfonium ylide intermediates is an important and widely used carbon-carbon bond forming reaction in organic synthesis. Wee and co-workers reported the diastereoselective rhodium (II) catalyzed sulfonium ylide formation and [2,3]-sigmatropic rearrangement reaction of chiral non-racemic allylic sulfides. The rearrangement reaction involves a concerted, orbital symmetry allowed, suprafacial process that generally proceeds with high stereoselectivity.

Scheme 25.
The chiral sulfide was prepared from the known allylic alcohol 118 which in turn was prepared from (E)-4-(4-chlorophenyl)-3-butene-2-one via reduction with borane-dimethyl sulfide catalyzed by (S)-2-Me-CBS reagent. Treatment of the alcohol 118 with bis(p-methoxyphenyl) disulfide and tributylphosphine under ultrasound irradiation yielded the secondary chiral sulfide 119. The Rh(II)-catalyzed reaction of 119 with ethyl diazoacetate provided an inseperable mixture of diastereomers 120, reductive desulfurization afforded 121. The double bond in 121 was subjected to ozonolysis/reduction sequence to furnish the corresponding primary alcohol. The alchohol was then subjected to lactonization catalyzed by PTSA to yield (R)-4-(4-chlorophenyl)-2-butyrolactone 122, a key intermediate used in the synthesis of the muscle relaxant and GABA receptor agonist (R)-4-(4-chlorophenyl)-2-butyrolactone, Scheme 25.

Chiral HPLC analysis of 122 however indicated the enantiomeric excess of the product was 63%. The low enantioselectivity of the product was unexpected. The author reasoned that partial racemization of the C-2 stereocenter must have occurred during the preparation of the sulfide 119 from the alcohol 118. The authors explain the partial racemization may involve the participation of solvent caged ion pair, under the Mitsunobu reaction condition, which would lead to the formation of 119 (the product of inversion) as the major product and its enantiomer (the product of retention) as the minor product.

4.2. Exploiting organocatalysis

In 2005 the pioneering work from Jorgensen’s laboratory revealed the enantioselective organocatalyzed α-sulfenylation of aldehyde, the first report of preparing chiral sulfides using proline mediated organocatalysis, Scheme 26.24

After screening many sulfonylating reagent and organocatalysts, compound 124 was found suitable in the presence of prolinol TMS ether 125.

Scheme 26.
4.2.1 Synthesis of vinyl glycines from chiral sulfides

In 2007 Armstrong and co-workers reported the enantioselective synthesis of vinyl glycines by allylic sulfilimine/[2,3] sigmatropic rearrangement from chiral sulfide which was prepared using the above protocol. Scheme 27.\textsuperscript{25}

Scheme 27.

\[
\begin{align*}
R-\text{CHO} & \xrightarrow{\text{Jorgensen's protocol}} \text{SnHex} \quad \text{R-CHO} \\
127 & \quad \Rightarrow \\
& \xrightarrow{\text{(EtO)}_2POCH_2CO_2Et, \text{nBuLi, DCM}} \text{SnHex} \quad \text{R-\text{CO}_2Et} \\
128 & \quad \Rightarrow \\
& \xrightarrow{\text{R} = \text{Me, Et, } \text{iPr, } \text{tBu, Bn, Allyl, } (\text{CH}_2)_2\text{OTBS}} \text{R-\text{CO}_2Et} \\
129 & 
\end{align*}
\]

The sensitive α-sulfinyl aldehydes 128 could be trapped by an in situ olefination, thus potentially offering a one-pot organocatalytic route to a range of chiral α-branched allylic sulfides 129. With a successful one-pot synthesis of enantiomerically enriched allylic sulfide accomplished, they explored the scope of the reaction by employing several commercially available aldehydes to provide many α-chiral sulfides.

With a versatile route to a range of enantioenriched (E)-allylic sulfides 129 in hand, they next tested them in the amidation/rearrangement reaction, Scheme 28. Chiral sulfide 130 reacted with novel oxaziridine 131 which was developed by the same group to furnish 133 essentially with complete chirality transfer.

Scheme 28.

\[
\begin{align*}
\text{SnHex} \quad \text{Me-\text{CO}_2Et} & \xrightarrow{\text{EtO}_2\text{C, DCM-78 ⁰C}} \text{SnHex} \quad \text{Me-\text{CO}_2Et} \\
130 & \quad \Rightarrow \\
& \xrightarrow{\text{rHex, } \text{S}^\ominus \text{Boc}} \text{rHexS}^\ominus \text{N}_\text{Boc} \quad \text{Me-\text{CO}_2Et} \\
131 & \quad \Rightarrow \\
& \xrightarrow{\text{Me-\text{CO}_2Et}} \text{Me-\text{CO}_2Et} \\
132 & \quad \Rightarrow \\
& \xrightarrow{\text{HexrS}^\ominus \text{N}_\text{Boc}} \text{HexrS}^\ominus \text{N}_\text{Boc} \quad \text{Me-\text{CO}_2Et} \\
133 & \quad \Rightarrow \\
& \xrightarrow{\text{P(OEt)}_3, \text{Et}_3\text{N}} \text{Me-\text{CO}_2Et} \\
134 & 
\end{align*}
\]

The vinyl glycine derivative 134 was obtained by a chemoselective cleavage of the S-N bond using triethylphosphite and triethylamine without affecting the double bond, α-stereocenter and allylic C-N bond.

Scheme 29.

\[
\begin{align*}
\text{HexrS}^\ominus \text{N}_\text{Boc} \quad \text{Me-\text{CO}_2Et} & \xrightarrow{\text{P(OEt)}_3, \text{Et}_3\text{N}} \text{Me-\text{CO}_2Et} \\
133 & \quad \Rightarrow \\
& \xrightarrow{\text{Me-\text{CO}_2Et}} \text{Me-\text{CO}_2Et} \\
134 & 
\end{align*}
\]
5. Present work

Introduction

The development of new and highly selectivity carbon-carbon, carbon-oxygen and carbon-nitrogen bond forming processes are an important topic in organic synthesis. The creation of stereogenic centers in an acyclic system, as compared to cyclic systems, is particularly challenging due to the many available degrees of freedom. Chiral α-branched propargylic and allylic sulfides are versatile building blocks and they act as a source of epoxy alkynes, epoxydienes, allylic alcohols, allylic amino derivatives and γ,δ-unsaturated acids.

It is clear from earlier discussion that very few protocols are available for the preparation of α-substituted sulfides and that too with limitations. In the route to chiral α-substituted sulfides from the chiral pool starting materials one enantiomer becomes more available than the other thus limiting the products that can be prepared. Also this method suffered from poor enantio purity of the prepared α-substituted sulfides. An exception to this is the recent report by Armstrong and co-workers on the preparation of allylic sulfides by employing Jorgensen’s proline derived organocatalysts for α-sulfenylation of aldehyde.

It is apparent that alternative approaches to secure chiral α-branched sulfides are greatly in demand to expand the scope of the process. To the best of our knowledge no synthesis of biologically active molecules were reported by using chiral α-substituted sulfides. We turned our attention to an alternate strategy for synthesizing chiral α-substituted sulfides from α-chloro sulfides via 1,2 asymmetric induction, and exploit them as useful intermediate for the synthesis of biologically active molecules.

5.1. Preparation of starting material

The investigation started with a simple sulfide which was prepared by copper-catalyzed 1,2 hydroxysulfoxidation of an alkene using a disulfide using Taniguchi’s protocol, Scheme 30.

Scheme 30.

The reaction between styrene 135 and diphenyl disulfide 136 in the presence of Cul (5 mol %), bpy (5 mol%) in the mixture of DMF-acetic acid as the solvent at 90 °C under oxygen
atmosphere provided the acetoxy sulfanyl compound 137 in good yield. The commercially available diphenyl disulfide 136 can be readily prepared from thiophenol and DMSO.

**Scheme 31.**

A plausible reaction mechanism

![Diagram of reaction mechanism]

The acetoxy sulfide 137 was hydrolyzed with 10 mol% of K₂CO₃ in methanol to furnish the hydroxy sulfide 139 in 95% yield. The free hydroxyl group of 139 was protected as its tert-butyldimethylsilyl ether by reaction with TBS-Cl and imidazole in DCM as the solvent, Scheme 32. The structure of the compound 140 was confirmed by its PMR spectrum, which showed signals at δ 4.95 (dd) for -CH(OTBS), 3.40 (dd), and 3.27 (dd) for S-CH₂-. Further the ESI mass spectrum showed the molecular ion peak at 367 [M+Na]⁺ confirming its identity.

**Scheme 32.**

![Chemical reactions]

**5.2 Feasibility study**

With the β-substituted sulfide 140 in hand, we began our investigations to obtain the corresponding α-substituted sulfide. Theoretically this can be done in two steps. First the sulfide has to be converted to a α-chlorosulfide, second the unstable, reactive α-chlorosulfides has to be carefully treated with a suitable nucleophile. The general reaction scheme is depicted below:
Scheme 33.

![Scheme 33 Image]

To access the product successfully, we turned our attention to the optimization of three factors, that included 1) chlorinating agent, 2) nucleophile and 3) solvent.

According to literature precedent carbon tetrachloride as the solvent and N-chlorosuccinimide as the chlorinating agent were found to be suitable for generating α-chlorosulfides. So we began by using N-chlorosuccinimide in CCl₄ to generate α-chlorosulfides. The reaction was completed within 30 min as judged by the TLC examination. Also succinimide was observed floating on top of carbon tetrachloride, supporting the conversion of sulfide to α-chlorosulfide 141. Removal of the solid succinimide by careful filtration under inert atmosphere furnished the clear α-chlorosulfide 141 solution in CCl₄. This was then treated with hexynylmagnesium bromide 143 in THF which was in turn prepared by treating 1-hexyne with EtMgBr in THF, Scheme 34. But this reaction failed to deliver the desired product. 

Scheme 34.

![Scheme 34 Image]

The same result was observed by varying the temperature at which the chlorosulfide was prepared and the temperature at which it was reacted with hexynylmagnesium bromide. A complex product mixture resulted from the above trials. The more basic sp³ and sp² Grignard reagent such as alkylmagnesium bromide and alkenylmagnesium bromide were next explored. Experiments were done with vinylmagnesium bromide, ethylmagnesium bromide and again no desired product was obtained. Stronger nucleophiles than ethylmagnesium bromide, such as methyl lithium and butyl lithium also failed to deliver the desired product, Scheme 35. The
basicity of the nucleophile was assumed to be an important parameter and hence attention was turned to exploiting other organometallic reagent.

**Scheme 35.**

\[
\begin{align*}
\text{BrMgCl} & \quad \xrightarrow{\text{THF}} \\
\text{MgBr, THF} & \quad \xrightarrow{\text{No desired product}} \\
\text{EtMgBr, Ether} & \quad \xrightarrow{\text{No desired product}} \\
\text{MeLi or } \text{nBuLi} & \quad \xrightarrow{\text{THF}}
\end{align*}
\]

The less basic organozinc reagents were employed as nucleophiles. Vinylzinc chloride generated in situ by treating vinylmagnesium bromide and anhydrous ZnCl₂ in THF. This was reacted with α-chlorosulfide 141 prepared in CCl₄. The results are summarized in Scheme 36. Once again alkynyl, alkenyl, alkylzinc chloride reagents failed to provide the desired α-substituted sulfide.

**Scheme 36.**

\[
\begin{align*}
\text{ZnCl} & \quad \xrightarrow{\text{EtZnCl}} \\
\text{EtZnCl} & \quad \xrightarrow{\text{No desired product}} \\
\text{ClZnCl} & \quad \xrightarrow{\text{Thio derivative}}
\end{align*}
\]

Having been unsuccessful in effecting C-C bond formation under a variety of conditions detailed above, it was decided to study the reaction on a much simpler substrate possessing no β-substituent. The simple sulfide 145 was prepared in a single step from commercially available 3-phenyl propanol 144, Scheme 37. The hydroxyl group of 144 was converted to the corresponding thio derivative by reacting with diphenyl disulfide in the presence of tributylphosphine.

**Scheme 37.**

\[
\begin{align*}
\text{Ph} & \quad \xrightarrow{\text{PhSSPh, Bu₃P}} \\
\text{OH} & \quad \xrightarrow{\text{toluene, 82%}} \\
\text{144} & \quad \xrightarrow{\text{145}}
\end{align*}
\]
Attempted preparation of α-substituted sulfide 147 using a variety of nucleophiles failed to afford any desired product. The results are tabulated in Table 1.

Scheme 38.

![Scheme 38](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R-MX</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>146</td>
<td>MgBr</td>
<td>No desired product</td>
</tr>
<tr>
<td>2</td>
<td>146</td>
<td>ZnCl</td>
<td>No desired product</td>
</tr>
<tr>
<td>3</td>
<td>146</td>
<td>Li</td>
<td>No desired product</td>
</tr>
<tr>
<td>4</td>
<td>146</td>
<td>BrMg</td>
<td>No desired product</td>
</tr>
<tr>
<td>5</td>
<td>146</td>
<td>ClZn</td>
<td>No desired product</td>
</tr>
</tbody>
</table>

Therefore steric hindrance due to -OTBS group could be ruled out as a possible reason for failure in the case of sulfide 140.

It was then decided to change the solvent from CCl₄ to benzene for the preparation of chlorosulfide. Sulfide 140 on treatment with NCS in anhydrous benzene furnished the α-chlorosulfide, within 30 min as judged by TLC examination which revealed the absence of starting material. As benzene has less density than NCS and succinimide, both settled at the bottom of the RB flask. Filtration was not necessary to remove the succinimide. The supernatant layer was transferred to another round bottom flask through a cannula. This α-chlorosulfide was then treated with vinylmagnesium bromide in THF at rt. Satisfyingly, the desired product was obtained but in very low yield (< 20% yield).

5.3 Optimization Study

Confidence was gained from the above results and attention was then focused on improving the yield. Some optimization study was done with various nucleophiles and the results are tabulated in Table 2.
Table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile(R-MX)</th>
<th>Product</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{MeLi} )</td>
<td>(140)</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{BuMgBr} )</td>
<td>(149)</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{BuMgBr} )</td>
<td>(150)</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{MgBr} + \text{ZnCl}_2)</td>
<td>(148)</td>
<td>45%</td>
</tr>
<tr>
<td>5</td>
<td>(\text{BuMgBr} )</td>
<td>(149)</td>
<td>50-55%</td>
</tr>
<tr>
<td>6</td>
<td>(\text{BuLi} )</td>
<td>(151)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>(\text{MeLi} )</td>
<td>(151)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) In all the reaction eliminated product was observed

From these experiments it was clearly understood that the nucleophile plays an important role. The less basic nucleophiles gave more of the desired product and less of the eliminated...
product and vice versa. The more basic butyl lithium and methyl lithium furnished only eliminated product and the less basic organozinc reagent provided the desired product, but yields were moderate. Zinc chloride was then replaced with zinc bromide to prepare the corresponding organozinc bromides. Interestingly the yield improved from 45% to 70%. The yield of the eliminated product were no more significant. The structure of the product 148 was confirmed by its PMR spectrum, which showed peaks at δ 5.85 (dd) characteristic for the internal olefinic proton, 5.1-4.9 (m, 3H) for the terminal olefinic protons and the -CH(OTBS). Also the disappearance of one of the S-CH$_2$ was observed. The ESI mass spectrum of 148 further supported its structure, that showed a molecular ion peak at 387 [M+NH$_4$]$^+$. 

To further avoid/minimize the obtention of elimination and other side products the relative ratio of benzene to THF was varied, the former used for preparing the chlorosulfide and the latter for organozinc reagent. Initially a 1:1 ratio of benzene and THF was used. For example 0.5 mmol of chlorosulfide was prepared in 5 mL of benzene (0.1 M) and 1-octyne (1.5 mmol, 3 eq) in THF (1.5 mL, 1 M) was treated with 1.5 mL of EtMgBr (1.5 mmol, 1M in THF, 3 eq) was added. After 30 min of stirring at 0°C 2 mL of ZnBr$_2$ solution (1 M in THF, 2 mmol) was added. A total of 5 mL of THF was used. The quantity of THF was reduced by taking neat 1-octyne (1.5 mmol) in round bottom flask and treating it with 1.5 mL of EtMgBr (1.5 mmol, 1M in THF, 1.5 mmol) and 1 mL of ZnBr$_2$ solution (1.5 M in THF, 1.5 mmol). Totally 2.5 mL of THF was used and the relative ratio of benzene to THF was 2:1. Using the above ratio of solvents the product was obtained in 80% yield without any side products. The reaction was repeated with various organozinc reagents in a 1:0.5 ratio of benzene and THF. After overnight stirring at rt, aqueous workup the crude material was characterized by NMR spectroscopy. The spectrum did not show any eliminated product and only the α-substituted sulfide was observed.

After performing these optimizations the selectivity of the reaction could be analyzed readily by examined of crude $^1$H NMR spectrum. The reaction of 1-octynylzinc bromide with 141 a 9:1 ratio of isomer was observed. In the case of vinylzinc bromide and butylzinc bromide afforded no other isomer was observed in the crude NMR spectrum.

Zinc bromide was prepared as a 1.5 M solution in THF by reacting excess of zinc dust with an equivalent of anhydrous 1,2-dibromoethane and stored by for future use. 31 This ZnBr$_2$ solution worked well for a month without loss of reactivity and provided a good yield everytime. The alkenyl Grignard reagents were prepared following the protocol devised by Knochel from 1-
iodo alkenes by metal-halogen exchange using \( {\text{iPrMgCl.LiCl}} \). The \( {\text{iPrMgCl.LiCl}} \) was prepared following the literature procedure using freshly distilled \( {\text{iso-propyl chloride}} \) and activated magnesium in anhydrous THF in presence of activated LiCl.\(^{32}\) Interestingly, the yields of propargyl sulfide 149 obtained by preparing the alkynyl Grignard using \( {\text{iPrMgCl.LiCl}} \) was better than using \( {\text{n-BuMgBr}} \) under otherwise identical conditions, Scheme 40.

Scheme 40.

Chlorosulfide 141 was subsequently reacted with organozinc reagents prepared from the silyl ether of propargyl alcohol and TMS acetylene, Scheme 41. The results are tabulated in Table 3. TMS acetylene gave better selectivity than 1-octyne and propargyl silyl ether. This may be described to the steric bulky of “TMS” group.

Scheme 41.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-ZnBr</th>
<th>Product</th>
<th>Yield</th>
<th>Selectivity(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BrZn</td>
<td>149</td>
<td>86</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>BrZn</td>
<td>152</td>
<td>76</td>
<td>9:1</td>
</tr>
<tr>
<td>3</td>
<td>BrZn</td>
<td>153</td>
<td>90</td>
<td>&gt;95:&lt;5</td>
</tr>
</tbody>
</table>

\(^a\) Determined from crude \( {\text{\( ^1 \)H NMR spectrum.}} \)

After sp hybridized organozinc reagents, \( {\text{sp^2}} \) and \( {\text{sp^3}} \) hybridized organozinc reagents were investigated, Scheme 42. For this commercially available Grignard reagents were explored, Table 4.
Scheme 42.

![Scheme 42](image)

Table 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-ZnBr</th>
<th>Product</th>
<th>Yield %</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>148</td>
<td>80</td>
<td>&gt;95:&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>154</td>
<td>-</td>
<td>-</td>
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<td>3</td>
<td>3</td>
<td>155</td>
<td>90</td>
<td>&gt;95:&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>156</td>
<td>72</td>
<td>&gt;95:&lt;5</td>
</tr>
<tr>
<td>5</td>
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<td>64</td>
<td>&gt;95:&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>158</td>
<td>56</td>
<td>&gt;95:&lt;5</td>
</tr>
</tbody>
</table>

a) Determined from crude 1H NMR spectrum.
b) Reagent polymerized during organozinc bromide preparation.

c) Exceptionally, the organozinc reagent prepared from the Grignard reagent obtained from 2-bromo propene suffered polymerization and no desired product was obtained, entry 2. In case of butyl and iso-propylzinc bromide some eliminated product was also observed resulting in a lower yield of the desired product (Entry 6 and 7). This may be explained as being due to the more basic nature of sp³ hybridized nucleophile than sp² and sp nucleophile. The reaction was however, very stereoselective as understood from the inspection of the crude 1H NMR spectrum. From the above experiments it can inferred that bulkyness and basicity nucleophiles play an important role in determining the selectivity and yield respectively.

Geometrically pure iodoalkenes were prepared from 1-octyne following reported procedures, Scheme 43. Treatment of 1-octyne with DIBAL-H furnished the corresponding (E)-alane that on quenching with I₂ provided pure (E)-iodoocetene 159 after distillation, while treatment of 1-
octyne with HBBr₂Me₂S afforded (Z)-boronic acid that on treatment with I₂ provided pure (Z)-iodooctene 160 after distillation.

Scheme 43.

\[ \text{I}_2 - 74\% \text{ then I}_2, -78 \degree C,\text{THF, 70\%} \]

\[ \text{160} \xrightarrow{\text{HBBR₂SMe₂, CH₂Cl₂, Dibal-H/Hex₅₅ \degree C, 5 h}} \text{159} \]

\[ E- \text{ and } Z-\text{iodooctene 159 and 160 were treated with } i-\text{PrMgClLiCl at } -40 \degree C \text{ for 7 h and 24 h respectively to furnish the corresponding Grignard reagent. Addition of ZnBr₂ yielded the corresponding zinc reagent. The } \alpha-\text{chlorosulfide 141 was reacted with these reagents to provide pure } E- \text{ and } Z-\text{alkenyl substituted sulfides 162 and 164 without any double bond isomerization in 60\% yield cleanly, Scheme 44. The identity of compound 162 was confirmed with the aid of its } ^1\text{H NMR spectrum which showed peaks at } \delta 5.40-5.20 \text{ (m) for internal olefinic protons, 4.91 (d) for Ph-CH(OTBS) and the mass spectrum showed a molecular ion peak at } 477 [\text{M+Na}]^+ . \]

Scheme 44.

\[ \text{159} \xrightarrow{i-\text{PrMgBrLiCl/THF, 40 \degree C, 7 h, then ZnBr₂}} \text{BrZn} \xrightarrow{\text{Benzene, 16 h, 60\%}} \text{161} \xrightarrow{\text{162}} \]

\[ \text{160} \xrightarrow{i-\text{PrMgBrLiCl/THF, 40 \degree C, 24 h, then ZnBr₂}} \text{BrZn} \xrightarrow{\text{Benzene, 16 h, 60\%}} \text{163} \xrightarrow{\text{164}} \]

5.4. Assigning of configuration

The configuration of the newly created centre was assigned based on the coupling constant(s) value of the methine proton. Mitzel et al.²⁶ reported preparation of syn and anti substituted hydroxy sulfides and assigned configuration to the isomers based on the coupling constant of its methine protons. In the syn isomer the methine protons showed coupling constant between 6.0 Hz and 8.0 Hz while anti isomers showed smaller coupling constant (4.0 Hz-5.5 Hz).
To assign the relative configuration, the TBS ether in sulfide 149 was deprotected using TBAF in THF, Scheme 45. The coupling constant of methine proton of the major isomer 165 was 6.6 Hz and for minor isomer 166 it was 5.1 Hz. Thus the major isomer should possess a syn relationship between OR and SPh substituents. The structure of the other products were assigned based on analogy.

Scheme 45.

The observed stereoselectivity can be rationalized by invoking a model depicted in Scheme 46, wherein the nucleophile attacks the sulenium ion from the side opposite to the phenyl group.

Scheme 46.

Assignment of configuration

6. Application in organic synthesis

The products are versatile synthons with many applications in organic synthesis. A recent report details the use of propargylic sulfides for the enantioselective preparation of allenamides. Also they can be partially reduced to stereoselectively yield either the cis or the trans-allenic sulfides, Scheme 47 or completely reduce to the alkyl sulfides. An added advantage is that the sp hybridized nucleophiles are less basic compared to others, thereby side reactions are minimized and the reagent used in excess can be recovered and reused.
Scheme 47.

A sigmatropic reaction is a pericyclic reaction wherein the net result is that one σ-bond is converted to another σ-bond in an uncatalyzed intramolecular process. In this type of rearrangement reaction, a substituent moves from one part of a π-bonded system to another part in an intramolecular reaction with simultaneous rearrangement of the π system. Generally, the E-alkene will favor the formation of anti product, while Z-alkene will favor formation of syn product. The general scheme is depicted below.

Scheme 48.

The usefulness of allylic sulfide was demonstrated in the stereoselective preparation of the 1,4-diol derivative, a subunit present in annonaceous acetogenins, oxylinps etc. Sulfide 162 on treatment with with m-chloroperoxybenzoic acid in dichromethane followed by addition of triethylphosphite and warming the reaction mixture furnished allyl alcohol 174 in excellent yield. The identity of compound 174 was assigned based on its PMR spectrum which showed peaks at δ 5.80-5.65 (m) characteristic of internal olefinic protons, δ 5.16 (d) for Ph-CH(OTBS)- and absence of PhS-. Its mass spectrum showed a molecular ion peak at 380 [M+NH₄]⁺ also confirming its structure. Treatment with anhydrous chloramine-T afforded the allyl amino derivative 176 via sulfilimine, Scheme 49. The structure of the compound 176 was confirmed by its PMR spectrum which showed peaks at δ 5.70-5.55 (m) for olefinic protons, 2.49 (s) for aromatic methyl and its mass spectrum shows molecular ion peak at 641 [M+NH₄]⁺. Thus a hydroxy/amino substituent can be introduced stereoselectively at C4 relative to the siloxy substituent via consecutive 1,2- followed by 1,3-asymmetric induction resulting in a net 1,4-induction. Also the double bond in 162, 164, 174 and 176 further provides a useful handle for
It is noteworthy that from an appropriate trisubstituted alkenyl zinc reagent, quaternary stereogenic centers can be created by the [2,3]-sigmatropic rearrangement.

Scheme 49.

Rh(II)-carbene and Cu(I)-carbene can efficiently react with allylic sulfides to generate sulfur ylides, which can subsequently undergo [2,3]-sigmatropic rearrangement.\(^{37}\) It can generate tertiary sulfides, which are not easily available. The in situ formation of sulfur ylide by treatment of 162 with ethyl diazoacetate in the presence of catalytic amounts of \(\text{Rh}_2(\text{OAc})_4\)\(^{38}\) and subsequent rearrangement yielded a mixture of isomeric dienes 178 instead of the desired product, Scheme 50.

Scheme 50.
7. One pot synthesis of chiral sulfides

The reaction of vinyl alane prepared by DIBAL-H reduction of 1-octyne was attempted. While a complex product mixture resulted using an excess of anhydrous zinc bromide, the reaction proceeded cleanly in the presence of catalytic amount of ZnBr₂, Scheme 51.

Scheme 51.

To secure (Z)-isomeric alane, the protocol devised by Hoveyda and co-workers⁴⁹ was utilized. Phenylacetylene was converted to the corresponding alkynyl silane 180 and subsequently reacted with DIBAL-H in anhydrous hexane to provide the (Z)-isomeric alane 181. Reaction of 181 with chlorosulfide 141 furnished no desired product, Scheme 52 and it is reasoned that the bulky nature of TMS group at the α-position prevented nucleophilic attack.

Scheme 52.

8. Conclusion

In summary we have disclosed a very versatile method for the synthesis of chiral α-branched propargylic, allylic and alkyl sulfides. The methodology would be useful for the synthesis of natural products possessing a 1,4-diol, 1,4-amino alcohol subunits, tetrahydrofuran, pyrrolidine, pyran and piperidine rings from appropriate starting materials. The application of this methodology for the synthesis of bioactive target molecules is under investigation in the laboratory.
Experimental procedure:

**Compound 139:** To a solution of the acetylated compound 137 (2.72 g, 10 mmol) in methanol (30 mL) was added K₂CO₃ (0.69 g, 5 mmol) at rt and the mixture stirred at the same temperature for 30 min. Methanol was evaporated under reduced pressure and the crude product was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 10% EtOAc/hexanes (v/v) as the eluent to furnish the pure product 139 (2.2 g, 9.5 mmol) in 95% yield as a liquid. TLC Rᶠ = 0.24 (10 % EtOAc/hexanes); IR (KBr) 3426, 3060, 2923, 1582, 1480, 1443, 1301, 1085, 1055, 740, 696 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.70-7.30 (m, 10H), 4.53 (dd, J = 3.8, 9.3 Hz, 1H), 3.15 (dd, J = 3.8, 13.8 Hz, 1H), 2.92 (dd, J = 9.3, 13.8 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 142.08, 134.96, 129.81, 128.90, 128.32, 127.74, 126.43, 125.70, 71.56, 43.52; MS (ESI) 253 [M+Na]⁺; HRMS (ESI) m/z calcd for C₁₄H₁₄ONaS 253.0663; found 253.0657.

**Compound 140:** To a solution of the alcohol 139 (2.1 g, 9 mmol) in anhydrous DCM (27 mL) maintained at rt was added imidazole (1.4 g, 21.6 mmol) followed by TBS₂Cl (1.9 g, 10.8 mmol) and stirred for a period of 3 h. The reaction mixture was diluted with DCM (30 mL), washed successively with water (10 mL), brine (10 mL), dried over Na₂SO₄, and the solvent evaporated under reduced pressure to yield the crude product which was purified by column chromatography using hexanes to furnish the product 140 (2.9 g, 8.3 mmol) in 92% yield as a liquid. TLC Rᶠ = 0.32 (hexanes); IR (KBr) 3447, 2953, 2927, 2855, 1582, 1470, 1252, 1094, 1008, 775, 737, 694 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.70-7.30 (m, 10H), 4.53 (dd, J = 3.8, 9.3 Hz, 1H), 3.15 (dd, J = 3.8, 13.8 Hz, 1H), 2.92 (dd, J = 9.3, 13.8 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 142.08, 134.96, 129.81, 128.90, 128.32, 127.74, 126.43, 125.70, 71.56, 43.52; MS (ESI) 367 [M+Na]⁺; HRMS (ESI) m/z calcd for C₂₀H₂₉O₂SiS 361.1657; found 361.1653.
**Compound 145:** To a mixture of 3-phenyl propanol 144 (1.36 g, 10 mmol) and diphenyl disulfide (2.18 g, 10 mmol) in anhydrous toluene (30 mL) cooled at 0 °C was added \( n\)-Bu_3P (6 mL, 2 M in EtOAc, 12 mmol) and stirred at rt for 6 h. The solvent was evaporated and crude product was purified by column chromatography using hexanes/EtOAc (98:2, v/v) to yield product 145 (1.87 g, 8.2 mmol) in 82% yield as a oil. TLC \( R_f = 0.30 \) (4% EtOAc/Hexanes). \(^1\)H NMR (300 MHz, CDCl_3): \( \delta \) 7.34-7.18 (m, 10H), 2.87 (t, \( J = 6.8 \) Hz, 2H), 2.73 (t, \( J = 6.8 \) Hz, 2H), 2.02-1.89 (m, 2H). MS (ESI) 267 [M+Na]^+;

**General procedure for the preparation of \( \alpha \)-chloro sulfide from sulfide:**

To a solution of sulfide (0.5 mmol) in anhydrous benzene (5 mL) was added \( N \)-chloro succinimide (NCS, 75 mg, 0.55 mmol) at rt and stirred for 45 min at the same temperature. Stirring was discontinued and the clear supernatant solution of chloro sulfide was siphoned using a syring and used in the next step. The yield of the chloro sulfide was assumed to be quantitative.

**General Procedures for the Preparation of Organozinc reagents:**

**From Alkynes:** (Silyl ether of propargyl alcohol, 1-octyne and trimethylsilyl acetylene)

To a solution of alkyne (1.5 mmol) in anhydrous THF (0.5 mL) cooled at -10° C was added \( i\)-PrMgCl.LiCl (1 mL, 1.5 mmol, 1.5 M in THF) and stirred for 30 min at the same temperature. To the so generated Grignard reagent a solution of ZnBr_2 (1.0 mL, 1.5 mmol, 1.5 M in THF) was added at 0 °C and stirred for 30 min. **From commercially available Grignard reagents:** (Vinylmagnesium bromide, \( (E) \) and \( (Z) \)-1-propenylmagnesium bromide, \( (E) \) and \( (Z) \)-1-methylpropenylmagnesium bromide, 2-methylpropenyl magnesium bromide, butylmagnesium bromide and \( isopropl\)magnesium bromide). To a solution of Grignard reagent (2 mL, 1.5 mmol, 0.75 M in THF) cooled at -10 °C was added ZnBr_2 (1.0 mL, 1.5 mmol, 1.5 M in THF) stirred for 30 min at the same temperature. **From Haoalkenes (159 and 160):** \( (E) \) and \( (Z) \)-1-Iodo-1-octene: To a solution of \( (E) \) and \( (Z) \)-iodo compound 159 and 160 (1.5 mmol) in anhydrous THF (0.5 mL) cooled at -40° C was added \( i\)-PrMgCl.LiCl (1 mL, 1.5 mmol, 1.5 M in THF) and stirred for 7 h and 20 h respectively at the same temperature. To the so generated \( (E) \) and \( (Z) \)-Grignard reagent a solution of ZnBr_2 (1.0 mL, 1.5 mmol, 1.5 M in THF) was added at 0 °C and stirred for 30 min.
General procedure for the preparation of α–substituted sulfides.

To the organozinc reagent (1.5 mmol) prepared as above, maintained at 0 °C was added the solution of chloro sulfide (0.5 mmol) in benzene and the reaction mixture stirred gradually allowing it to attain rt and stirred further until TLC indicated complete consumption of the chloro sulfide (7-14 h). The reaction mixture was cooled to 0 °C and quenched by addition of an aqueous saturated NH₄Cl solution. It was allowed to warm to rt and diluted with ether. The layers were separated and aqueous layer extracted with ether. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using hexanes as the eluent to afford the pure product.

**Compound 148:** Similarly the chloro sulfide (0.5 mmol) was reacted with the organozinc reagent prepared from vinyl magnesium bromide (1.5 mmol) at rt for 6 h to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product 148 (148 mg, 0.4 mmol) in 80% yield as a liquid. TLC Rₕ = 0.32 (hexanes); IR (KBr) 3447, 3067, 2930, 2856, 1468, 1254, 1094, 840, 776 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.60-7.30 (m, 10H), 5.85 (ddd, J = 9.1, 10.5, 17.0 Hz, 1H), 5.1- 4.9 (m, 3H), 4.0 (dd, J = 7.8, 9.1 Hz, 1H), 1.05 (s, 9H), 0.2 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 141.85, 135.64, 132.18, 128.56, 127.66, 127.53, 127.13, 126.61, 116.9, 76.99, 61.63, 25.79, 18.48, -4.63, -5.00; MS (ESI) 387 [M+NH₄]⁺; HRMS (ESI) m/z calcd for C₂₂H₃₀ONaSiS 393.1678; found 393.1684.

**Compound 149:** To a solution of 1-octyne (165 mg, 1.5 mmol) in anhydrous THF (0.8 mL) cooled at -10 °C was added i-PrMgCl.LiCl (1 mL, 1.5 mmol, 1.5 M in THF) and stirred for 30 min at the same temperature. To the so generated Grignard reagent ZnBr₂ (1.1 mL, 1.65 mmol, 1.5 M in THF) was added at 0 °C and stirred for 30 min. To the organozinc reagent maintained at
0 °C was added a solution of chloro sulfide (0.5 mmol) in benzene (5 mL) and the reaction mixture stirred gradually allowing it to attain rt and stirred further for a period of 7 h when TLC examination indicated complete consumption of the chloro sulfide. The reaction mixture was cooled to 0 °C and quenched by the addition of an aqueous saturated NH₄Cl solution. It was allowed to warm to rt and diluted with ether (5 mL), the layers were separated and aqueous layer extracted with ether (3×10 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na₂SO₄ and the solvent evaporated under reduced pressure to afford a crude compound which was purified by column chromatography using hexanes as the eluent to afford the pure product **149** (192 mg, 0.43 mmol) in 86% yield as a liquid. TLC Rf = 0.34 (hexanes); IR (KBr) 3445, 3063, 2954, 2928, 1586,1463, 1384, 1253, 1094, 827, 837, 777,695 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.62-7.30 (m, 10H), 4.91 (d, J = 6.6 Hz, 1H), 4.16 (td, J = 2.3, 6.6 Hz, 1H), 2.16 (dt, J = 2.3, 6.6 Hz, 2H), 1.5-1.15 (m, 8H), 1.0-0.9 (m, 12H), 0.20 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 142.00, 135.62, 132.11, 128.58, 127.82, 127.69, 127.36, 126.89, 87.32, 77.45, 48.91, 31.45, 28.51, 28.47, 25.89, 22.62, 18.35, 14.20, -4.55, -4.83; MS (ESI) 469 [M+NH₄]⁺; HRMS (ESI) m/z calcd for C₂₈H₄₀ONaN₂SiS 475.2467; found 475.2466.

**Compound 150:** Following the general procedure the chloro sulfide (0.5 mmol) was reacted with n-butylzinc bromide (1.5 mmol) at rt for 10 h to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish **150** (130 mg, 0.32 mmol) in 64% yield as a liquid. TLC Rf = 0.40 (hexanes); IR (KBr) 3063, 2954, 2930, 2857, 1468, 1253, 1089, 837 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz,) δ 7.70-7.30 (m, 10H), 5.00 (d, J = 4.5 Hz, 1H), 3.42 (dt, J = 4.5, 9.1 Hz,1H), 2.0-1.4 (m, 6H), 1.1-1.0 (m, 12H), 0.20 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 142.02, 137.32, 130.75, 128.67, 127.48, 127.33, 127.23, 126.01, 76.33, 57.96, 30.76, 29.46, 25.78, 22.42, 18.15, 13.92, -4.69, -5.07; MS (ESI) 423 [M+Na]⁺; HRMS (ESI) m/z calcd for C₂₄H₃₆O₂NaSiS 439.2103; found 439.2105.

**Compound 152:** Following the general procedure α-chloro sulfide (0.5 mmol) was allowed to
react with organozinc reagent prepared from Silylether of propargyl alcohol (1.5 mmol) at rt for 7 h to afford a crude product after work up. Purification by column chromatography using hexanes as the eluent to afford the pure product **152** in (195 mg, 0.38 mmol) in 76% yield as a liquid; TLC \( R_f = 0.30 \) (hexanes); IR (KBr) 3062, 2954, 2930, 2890, 2857, 1717, 1468, 1365, 1254, 1087, 837, 777, 744, 696 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 200 MHz) \( \delta \) 7.6-7.3 (m, 10H), 5.00 (d, \( J = 6.0 \) Hz, 1H), 4.32 (s, 2H), 4.24 (d, \( J = 6.0 \) Hz, 1H), 1.00 (s, 9H), 0.90 (s, 9H), 0.20 (s, 6H), 0.10 (s, 6H); \(^1^3\)C NMR (CDCl\(_3\),75 MHz) \( \delta \) 141.61, 132.50, 132.04, 128.70, 127.93, 127.80, 127.30, 127.07, 84.94, 82.54, 76.97, 51.80, 48.81, 25.85, 18.32, 18.26, -4.60, -4.85, -5.15; MS (ESI) 530 \([M+NH_4]^+\); HRMS (ESI) m/z calcd for C\(_{29}\)H\(_{44}\)O\(_2\)NaSiS 535.2508; found 535.2498.

**Compound 153:** Similarly \( \alpha \)-chloro sulfide (0.5 mmol) was allowed to react with the organozinc reagent prepared from trimethylsilyl acetylene (1.5 mmol) at rt for 16 h to afford a crude product after work up. Purification by column chromatography using hexanes as the eluent furnish pure **153** (198 mg, 0.45 mmol) in 90% yield as a liquid. TLC \( R_f = 0.35 \) (hexanes); IR (KBr) 3063, 2956, 2931, 2857, 2175, 1471, 1252, 1096, 843, 777 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.6-7.3 (m, 10H), 4.94 (d, \( J = 6.7 \) Hz, 1H), 4.11 (d, \( J = 6.7 \) Hz, 1H), 1.03 (s, 9H), 0.20 (s, 3H), 0.14 (s, 9H), 0.0 (s, 3H); \(^1^3\)C NMR (CDCl\(_3\),75MHz) \( \delta \) 141.57, 134.77, 132.85, 128.49, 127.78, 127.56, 127.23, 103.10, 91.24, 76.91, 49.48, 25.76, 18.26, -0.32, -4.65, -4.93; MS (ESI) 458 \([M+NH_4]^+\); HRMS (ESI) m/z calcd for C\(_{25}\)H\(_{37}\)O\(_2\)Si\(_2\)S 457.2052; found 457.2054.

**Compound 155:** Similarly the chloro sulfide (0.5 mmol) was reacted with the organozinc reagent prepared from mixture of (\( E \)) and (\( Z \))-1-propenylmagnesium bromide (1.5 mmol) at rt for 6 h to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish the pure product **155** (172mg, 0.45 mmol) as an inseparable mixture of (\( E \)) and (\( Z \)) isomer in 90% yield as a liquid. TLC \( R_f = 0.28 \) (hexanes); IR (KBr) 3450, 3063, 2928, 2856, 2367, 1466, 1253, 1091, 837, 774, 695.3 cm\(^{-1}\); **Major E isomer:** \(^1\)H NMR (CDCl\(_3\),400
Chapter-I

MHz) δ 7.6-7.2 (m, 10H), 5.50-5.25 (m, 2H), 4.92 (d, J = 5.5 Hz, 1H), 3.89 (dd, J = 5.5, 8.6 Hz, 1H), 1.68 (d, J = 6.3 Hz, 3H), 1.05 (s, 9H), 0.2 (s, 3H), 0.0 (s, 3H); **Minor Z isomer**: ¹H NMR (CDCl₃, 400 MHz) δ 7.6-7.2 (m, 10H), 5.50-5.25 (m, 2H), 4.86 (d, J = 6.3 Hz, 1H), 4.36 (dd, J = 6.3, 10.2 Hz, 1H), 1.31(d, J = 7.1 Hz, 3H), 1.08 (s, 9H), 0.19 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz ) δ 142.10, 135.51, 132.73, 132.10, 128.67, 128.41, 128.29, 128.06, 127.58, 127.39, 127.33, 127.12, 126.69, 126.37, 126.27, 77.41, 60.65, 54.72, 25.77, 18.20, 17.60, 12.68, -4.68, -5.03; MS (ESI) 401 [M+NH₄]⁺; HRMS (ESI) m/z calcd for C₂₃H₃₂O₂NaSiS 423.1790; found 423.1804.

**Compound 156**: Similarly the chloro sulfide (0.5 mmol) was reacted with the organozinc reagent prepared from mixture of (E) and (Z)-1-methyl-1-propenylmagnesium bromide (1.5 mmol) at rt for 6 h to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnished the pure product 156 (143 mg, 0.36 mmol) as inseparable mixture of (E) and (Z) isomer in 72% yield as a liquid. TLC Rf = 0.32 (hexanes); IR (KBr) 3451, 3063, 2928, 2856, 1593, 1495, 1259, 832 cm⁻¹; Major E isomer ¹H NMR (CDCl₃, 200 MHz,) δ 7.6-7.3 (m, 10H), 5.12 (m, 1H), 4.95 (d, J = 9.1 Hz, 1H), 4.76 (d, J = 9.1 Hz, 1H), 1.89 (s, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.08 (s, 9H), 0.20 (s, 3H), 0.0 (s, 3H); Minor Z isomer ¹H NMR (CDCl₃, 200 MHz) δ 7.6-7.3 (m, 10H), 5.12 (m, 1H), 4.95 (d, J = 9.1 Hz, 1H), 4.76 (d, J = 9.1 Hz, 1H), 1.76 (s, 3H), 1.49 (d, J = 7.0, 3H), 1.08 (s, 9H), 0.20 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75MHz ) δ 142.77, 136.34, 132.06, 131.80, 131.65, 128.24, 127.68, 127.52, 126.32, 124.45, 76.56, 58.43, 25.80, 19.73, 18.30, 12.93, -4.61, -4.90; MS (ESI) 421 [M+Na]⁺; HRMS (ESI) m/z calcd for C₂₄H₃₄O₂NaSiS 437.1946; found 437.1951.

**Compound 157**: Similarly the chloro sulfide (0.5 mmol) was reacted with the organozinc reagent prepared from 2-methyl-1-propenylmagnesium bromide (1.5 mmol) at rt for 6 h to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish pure 157 (149 mg, 0.38 mmol) in 76% yield as a liquid. TLC Rf = 0.30 (hexanes); IR
(KBr) 3435, 3028, 2955, 2928, 2856, 2360, 1470, 1254, 1091, 837, 774, 696 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.6-7.3 (m, 10H), 5.10 (d, J = 10.3 Hz, 1H), 4.84 (d, J = 5.9 Hz, 1H), 4.24 (dd, J = 5.9, 10.3 Hz, 1H), 1.68 (s, 3H), 1.30 (s, 3H), 1.05 (s, 9H), 0.20 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 142.36, 135.87, 134.60, 132.70, 128.31, 127.51, 127.11, 126.49, 122.90, 77.71, 56.18, 25.79, 25.47, 18.27, 17.79, -4.66, -5.01; MS (ESI) 321 [M+Na]+; HRMS (ESI) m/z calcd for C₂₄H₃₄ONaSiS 421.1999; found 421.1997.

**Compound 158:** Similarly the chloro sulfide (0.5 mmol) was reacted with isopropylzinc bromide (1.5 mmol) at rt for 10 h to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish 158 (116 mg, 0.3 mmol) in 60% yield as a liquid. TLC R₇ = 0.38 (hexanes); IR (KBr) 3062, 2955, 2928, 2856, 1538, 1469, 1252, 1089, 770 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.50-7.00 (m, 10H), 4.80 (d, J = 6.6 Hz, 1H), 3.10 (dd, J = 4.4, 6.6 Hz, 1H), 1.85-1.70 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 5.8 Hz, 3H), 0.80 (s, 9H), 0.20 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 143.53, 139.10, 130.22, 128.46, 127.92, 127.38, 126.99, 125.48, 76.69, 66.77, 29.76, 25.76, 21.95, 18.38, 18.14, -4.55, -4.90; MS (ESI) 409 [M+Na]+; HRMS (ESI) m/z calcd for C₂₃H₃₄O₂NaSiS 425.1946; found 425.1931.

**Compound 162:** To a solution of (E)-1-iodo-1-octene (360 mg, 1.5 mmol) in THF (0.6 mL) was slowly added i-PrMgCl·LiCl (1.1 mL, 1.65 mmol, 1.5 M in THF) at -40 °C and stirred for 7 h, raise temperature to 0 °C, ZnBr₂ (1.1 mL, 1.65 mmol, 1.5 M in THF) was added stirred for 30 min at the same temperature. Following the general procedure chloro sulfide (0.5 mmol) was reacted with (E)-1-octenylzinc bromide (1.5 mmol) at rt for 16 h to afford a crude product after work up. Purification by column chromatography using hexane as the eluent furnished pure 162 (136 mg, 0.3 mmol) in 60% yield as a liquid. TLC R₇ = 0.30 (hexanes); IR (KBr) 3062, 2955, 2928, 2856, 1742, 1583, 1463, 1362, 1253, 1093, 1026, 837, 776, 746, 696 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.6-7.2 (m, 10H), 5.4-5.2 (m, 2H), 4.91 (d, J = 6.0 Hz, 1H), 3.91 (dd, J= 6.0, 8.3 Hz, 1H), 2.0-1.8 (m, 2H), 1.5-1.2 (m, 8H), 1.2-1.0 (m, 12H), 0.2 (s, 3 H), 0.0 (s, 3H); ¹³C
NMR (CDCl$_3$, 75 MHz) $\delta$ 142.10, 133.78, 132.43, 132.33, 128.37, 128.70, 127.53, 127.11, 126.40, 125.75, 77.34, 60.73, 32.11, 31.65, 31.65, 28.99, 28.50, 25.78, 22.52, 18.21, 14.07, -4.66, -5.00; MS (ESI) 477 [M+Na]$^+$; HRMS (ESI) $m/z$ calcd for C$_{28}$H$_{42}$O$_2$NaSiS 493.2872; found 493.2876.

**Compound 164:** Following the general procedure the chloro sulfide (0.5 mmol) was reacted with the organozinc reagent prepared from (Z)-iodo-octene to afford the crude product which was purified by column chromatography using hexanes as the eluent to furnish 164 (136 mg, 0.3 mmol) in 60% yield as a liquid. TLC $R_f$ = 0.32 (hexanes); IR (KBr) 3425, 2925, 2855, 1747, 1538, 1463, 1365, 1253, 1215, 1092, 837, 770, 696 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.6-7.2 (m, 10H), 5.40-5.30 (m, 2H), 4.83 (d, $J$ = 6.8 Hz, 1H), 4.32 (dd, $J$ = 6.8, 9.9 Hz, 1H), 1.7-1.6 (m, 2H), 1.40-1.10 (m, 8H), 1.05-1.0 (m, 12H), 0.20 (s, 3H), 0.0 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) 142.31, 142.11, 133.83, 133.05, 132.39, 128.40, 127.61, 127.41, 127.12, 126.75, 77.64, 55.53, 31.67, 29.12, 28.88, 27.43, 25.80, 22.52, 18.28, 14.07, -4.62, -4.99; MS (ESI) 477 [M+Na]$^+$; HRMS (ESI) $m/z$ calcd for C$_{28}$H$_{42}$O$_2$NaSiS 493.2872; found 493.2876.

**Compound 174:** To a solution of 162 (45 mg, 0.1 mmol) in DCM (1 mL) cooled at -78 °C was added mCPBA (25 mg, 0.11 mmol) and the reaction mixture stirred at the same temperature for another 45 min. Methanol (0.5 mL) and triethyl phosphite (0.16 mL, 1 mmol) was added and the temperature allowed to rise to 60° C and stirred further for 1 h. The reaction was quenched by adding aqueous saturated NaHCO$_3$ (0.5 mL). The mixture was diluted with DCM (4 mL) and the layers separated. The organic layer was washed successively with water (1 mL), brine (1 mL), dried over Na$_2$SO$_4$ and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 5% EtOAc/hexanes (v/v) as the eluent to afford the product 174 (29 mg, 0.08 mmol) in 80% yield as a liquid. TLC $R_f$ = 0.32 (5% EtOAc/Hexanes); IR (KBr) 3448, 2926, 2855, 1630, 1462, 1254, 1217, 1060, 837, 767, 697 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.6-7.2 (m, 5H), 5.80-5.65 (m, 2H), 5.16 (d, $J$ = 2.9 Hz, 1H), 4.2-4.1 (m, 1H), 1.5-1.4 (m, 2H), 1.3-1.1 (m, 8H), 1.0-0.9 (m, 12H), 0.20 (s, 3H), 0.0 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 143.78, 134.40, 132.04, 128.15, 126.98, 125.86, 74.83, 72.39,
37.11, 31.74, 29.13, 25.83, 25.30, 22.52, 18.32, 14.04, -4.57, -4.82; MS (ESI) 380 [M+NH₄]⁺; HRMS (ESI) m/z calcd for C₂₂H₃₈O₂NaSi 385.2538; found 385.2544.

**Compound 176:** To a solution of 162 (45 mg, 0.1 mmol) in DCM (1 mL) maintained at rt was added anhydrous chloramine-T (28 mg, 0.12 mmol) and the mixture stirred for 3 h. The solvent was removed under reduced pressure and the residue purified by column chromatography using 5% EtOAc/hexanes (v/v) as the eluent to furnish the product 176 (48 mg, 0.078 mmol) in 78% yield as a liquid. TLC Rf = 0.36 (5% EtOAc/Hexanes); IR (KBr) 3445, 2953, 2928, 2856, 1596, 1469, 1355, 1164, 1092, 838, 775, 669 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.82-7.2 (m, 14H), 5.72-5.55 (m, 2H), 5.06 (bs, 1H), 4.72-4.6 (m, 1H), 2.49 (s, 3H), 1.62-1.1 (m, 10H), 1.00-0.90 (m, 12H), 0.20 (s, 3H), 0.0 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ 143.58, 143.28, 138.56, 136.84, 136.61, 129.36, 128.70, 128.07, 127.81, 127.08, 126.91, 125.89, 74.36, 64.13, 31.54, 28.71, 26.00, 25.77, 22.40, 21.53, 18.23, 14.01, -4.80, -4.95; MS (ESI) 641 [M+NH₄]⁺; HRMS (ESI) m/z calcd for C₃₅H₄₉NO₃NaSiS₂ 646.2820; found 646.2800.

**Compound 162 (one pot synthesis):** To a solution of 1-octyne (0.23 mL, 1.5 mmol) in anhydrous hexane (1.5 mL) cooled at 0 °C was added DIBAL-H (1.07 mL, 1.4 M in toluene, 1.5 mmol) dropwise for 5 min and the temperature raised to 55 °C and stirred for 5 h. To the resulting E-octenyl alane solution was added ZnBr₂ (0.08 mL, 1.5 M in THF, 0.12 mmol), stirred for 30 min. A solution of chlorosulfide 141 in benzene (0.5 mmol) was added at 0 °C and stirred for 7 h at rt. The reaction mixture was quenched with aq saturated NH₄Cl and dilute with ether. The layers were separated and the aq layer was extracted with ether (2×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and the solvent evaporated to afford a crude product which was purified by column chromatography using EtOAc/hexanes (10% v/v) to provide 162 (168 mg, 0.37 mmol) in 74% yield.

**References:**

Section II

Chiral substituted sulfides using asymmetric catalysis and chiral auxiliary

1. Brief introduction

Most asymmetric catalysts that have been developed so far are metal complexes with chiral organic ligands. The chiral ligand modifies the reactivity and selectivity of the metal center in such a way that one of two possible enantiomeric products is formed preferentially. Based on this concept, many metal complexes have been found that catalyze various reactions with impressive enantioselectivity. Catalytic methods are often preferred due to the potential for recycling the catalyst and the small amounts of chiral material required. Furthermore, catalysts which are able to participate in a secondary interaction with substrates, in a substrate-catalyst complex, are highly valued as they have been observed to promote efficient asymmetric induction. Asymmetric catalytic reactions are the most important synthetic method because of their broad scope and efficiency (i.e. selectivity and atom economy). Among the most popular asymmetric ligands are Binol, Binap, Bis[oxazoline], Taddol ligand, Salen and cinchona alkaloid among others.

2. Present Work

The C-C bond formation with simultaneous creation of a new stereogenic center is an important objective. In the previous section α-substituted sulfides were prepared from α-chlorosulfides via 1,2-induction by a β-substituent. The next task was to attempt and synthesize chiral substituted sulfide using chiral ligands.

The catalytic asymmetric alkynylzinc addition to aldehyde provides a convenient route to the chiral propargylic alcohol. A great deal of effort has recently been directed towards the development of this important asymmetric reaction and two general catalytic systems are currently considered to be the most practical. One of the methods was discovered by Carreira using Zn(OTf)$_2$ as the catalyst, N-methyl ephedrine (NME) as the chiral ligand and triethylamine as the base. Another method involves the use of Me$_2$Zn or Et$_2$Zn to prepare the alkynylzincs in situ in presence of chiral Binol and Ti(OiPr)$_4$. It was decided to explore the above methods as a route to prepare chiral propargyl sulfides by reaction of alkynylzinc reagent with α-chlorosulfide.
2.1. Exploiting Carreira’s protocol

Initially the reaction was attempted exploiting Carreira’s protocol using 1-octyne, (+)-NME and Et$_3$N with α-chlorosulfide 146 which was prepared from sulfide 145 under standard conditions. The product 182 was obtained in poor yield (20%) at room temperature, Scheme 53. Its structure was assigned based on its PMR spectrum which showed peaks at δ 3.82-3.64 (m) for -SCH- and 0.94 (t) for -CH$_3$. The optical purity however could not be estimated because peak separation of enantiomers of racemic compound 182 prepared using iPrMgCl.LiCl and ZnBr$_2$, was not observed using different chiral columns (AS-I, OB and OD). The reaction was next attempted using silyl ether of propargyl alcohol. The expected product 183 was indeed obtained in 24% yield. The structure was assigned to 183 by its $^1$H NMR spectrum which showed peaks at δ 4.33 (s) for -CH$_2$OTBS, 3.73 (t) for -SCH-, and 0.93 (s), 0.05 (s) for TBS group. The enantiomers of racemic compound 183 could be separated by chiralcel OD column (10% iPrOH/hexane (v/v) and flow rate was 0.5 mL/min). The two enantiomers eluted at 12.8 and 22.9 min. The compound obtained using Carreira’s protocol revealed a 58:42 ratio of enantiomers.

The reaction was attempted using CH$_2$Cl$_2$ as the solvent for generating chlorosulfide instead of benzene when a slight improvement was observed in both the yield (36%) and selectivity (79:21). The reaction was attempted in chlorobenzene and methylcyclohexane as solvents to generate the chlorosulfide, but no improvement in yield and selectivity was noted when compared to using benzene/dichloromethane as the solvent.

Scheme 53.
The reaction was run at low temperature with the expectation of enhancing the selectivity, but it did not bear fruit. Prolonged reaction at 0 °C resulted in a complex mixture as revealed by the crude PMR spectrum.

The reaction when attempted with reactive phenyl acetylene delivered the corresponding product 184 in a modest yield (42% yield), Scheme 54. The structure of 184 was assigned with the aid of its $^1$H NMR spectrum which showed peaks at 3.92 (t) for -SCH- proton and fifteen protons in the aromatic region. The two enantiomers of racemic 184 could be separated on a chiral AS-I column (hexane/iPrOH: 99:1, v/v, flow rate: 1 mL/min), one of the enantiomers eluted at 4.7 min and the other at 5.1 min. The enantiomer ratio of the compound 184 was determined to be 68:32.

Scheme 54.

![Scheme 54](image)

2.2. Exploiting Pu’s protocol

The reaction was next attempted using Pu’s protocol. The chlorosulfide 146 was treated with the silyl protected propargyl alcohol and phenyl acetylene in the presence of (R)-Binol, Ti(OiPr)$_4$, HMPA and Et$_2$Zn to afford products 183 and 184 respectively in modest yield. The enantiomer ratio was determined to be around 6:4, Scheme 55. The reactions in a variety of solvents and at low temperatures did not facilitate to enhance the yield and selectivity.

Scheme 55.

![Scheme 55](image)
3. Conclusion:

Suitable conditions could not be developed to elaborate chiral α-substituted sulfides using the limited protocols explored. Further exploration of chiral complexes is called for.

4. Brief introduction to a chiral auxiliary

The auxiliary is a chiral moiety that is attached to a prochiral substrate molecule, thus creating an asymmetric environment around the substrate. This molecule is then able to undergo a reaction where the very nature of the auxiliary induces some measure of stereocontrol in the formation of products. Removal of the auxiliary then affords a chiral product. Requirements for a chiral auxiliary include: a) ready availability as a homochiral moiety that can be easily attached to the prochiral substrate, b) capacity to induce a high degree of stereoselectivity, c) easy removal from the product and recoverability in high yield.

Today an arsenal of chiral auxiliaries are available meeting the above criteria in full or in part. Of the numerous chiral auxiliaries that have been developed over the past years some of the effectively applied auxiliaries are shown in Fig. 1. The majority of chiral auxiliaries are derived from inexpensive, chiral natural sources and most of the reactions reported proceed with high levels of diastereoselection.

Figure 1.

5. Present work

As illustrated in the preceding section chiral auxiliaries have stimulated a great deal of attention due to their utility in synthetic organic chemistry. Thus far no method is reported to synthesize chiral substituted sulfides using chiral auxiliary control.
5.1. Utilizing camphor based auxiliary

We initially explored camphor based auxiliary. Asymmetric induction in the reactions of various camphor derivatives is primarily due to the steric constraints resulting from the rigidity of the structure and the bulk of the 8-, 9- and 10- methyl groups. Initial attack on the camphor skeleton occurs, in most instances, from the less hindered endo-face to generate enantiomeric products.

Figure 2.

The chiral auxiliary 3-exo-thio-2-exo-hydroxy camphor 193 was prepared by a reported procedure in three steps. The synthesis began with the exo-sulfurization of camphor 189 using exactly 1 eq of LDA and phenylthiosylate 190. The thiosylate 190 was prepared in two steps from readily accessible tosyl chloride.

The resulting exo-sulfenyl ketone 191 was submitted to DIBAL-H reduction to give exo-alcohol 192 in high yield. The hydroxy group was protected as its benzoate using benzoyl chloride, Scheme 56. The structure of the compound 193 was confirmed by help of its $^1$H NMR spectrum which showed peaks at $\delta$ 5.06 (d) for -CH-OBz, 3.62 (s) for benzylic protons and 2.91 (d) for -CH-SBn.

Scheme 56.

The sulfide 193 was subjected to reaction with NCS and the resulting chlorosulfide treated with vinyzinc bromide, examination of the product NMR revealed the formation of a regioisomeric mixture of products 194 and 195 in roughly equimolar amounts, Scheme 57.
Scheme 57.

The structure of 194 and 195 were confirmed by the PMR spectrum. The $^1$H NMR of 195 revealed a peak at $\delta$ 6.22 for internal olefinic as a dd, 5.36-4.85 (m) integrating for three protons (terminal olefinic and -CHOBz), characteristically the -CH-S signal was absent. In the case of 194 the olefinic proton resonated at $\delta$ 5.78 (m) and 5.36-4.85 (m, 3H) for the -CHOBz and terminal olefinic protons. Interestingly, compound 195 was obtained with excellent selectivity whereas 194 was obtained as a 3:1 mixture of diastereomers. The endo configuration of the vinyl substituent in 195 is assumed based on steric consideration. The structure of the major diastereomer in 194 was not assigned.

Figure 3.

The formation of mixture of 194 may be explained by free rotation of carbon-sulfur bond due to which two different orientations of the sulfonium intermediate (II and III) can be envisioned, Figure 3. The vinylzinc bromide attacks each of these conformations from the less hindered rear side, resulting in diastereoisomers. In case of 195, the reaction is assumed to precede through the intermediate of sulfonium ion I.

To avoid the formation of tertiary $\alpha$-chlorosulfide NCS (0.9 eq) was added portionwise in regular interval of time. However, no significant improvement was observed. To avoid C3 chlorination it was intended to substitute the C3 hydrogen in 193 with a methyl group.
Scheme 58.

It was planned to prepare the chiral auxiliary 199 in a manner similar to that of 193, Scheme 58. But sulfurization of 196 afforded mixture of exo and endo isomers 197 in 7:3 ratio. After isolating the isomers, the major isomer was subjected to DIBAL-H reduction. The reduction proceeded stereo randomly to furnish the exo and endo isomers 198 in a nearly equimolar ratio. This sequence provided more than one isomer. Therefore, it was not synthetically useful and further study along this direction was stopped.

5.2. Utilizing menthol derived auxiliary

We next set out to utilize menthol derivative as the chiral auxiliary.\(^7\) The preparation of chiral auxiliary 204 commenced with commercially available (+)-pulegone 200.\(^8\) Michael addition of benzyl thiol to (+)-pulegone 200 followed by selective reduction of ketone using Li-liquid ammonia and methanol provided hydroxy thiol 202 in good yield. Michael addition of benzyl thiol using sodium hydride as the base following a reported procedure provided 201 in poor yield while reaction of benzyl thiol in the presence of DBU in anhydrous toluene afforded product 201 cleanly in high yield.\(^9\) The thiol in 202 was selectively protected as its benzyl ether and the carbinol was protected as its benzoate, Scheme 59. The structure of 204 was assigned from the \(^1\)H NMR spectrum which showed peaks at \(\delta\) 5.60-5.56 (m) for -CH-OBz, 3.66 (s) for -SCH\(_2\)Ph.
Scheme 59.

The chlorosulfide prepared from 204 was reacted with vinylzinc bromide following standard conditions. This reaction delivered the product in good yield with moderate selectivity (7:3). The reaction attempted with 2-methyl-propenylzinc bromide also afforded the product as a 3:1 ratio of diastereoisomers. The reaction with octynylzinc bromide and E-octenyl alane, prepared from 1-octyne and DIBAL-H, also provided the desired product in good yield with a 7:3 and 3:1 ratio of diastereoisomers respectively, Scheme 60. The results are summarized in Table 5. It is noteworthy that these chlorosulfides too failed to react with organozinc reagents at 0 °C. It is to be note of that the structure of the major diastereomer depicted is not unambiguously established but is assigned based on model.

Scheme 60.

Table 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chloro sulfide</th>
<th>R-ZnBr</th>
<th>Product</th>
<th>Yield$^a$ and Selectivity (dr)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>205</td>
<td>=<strong>C</strong>Br</td>
<td>206</td>
<td>64% and 7:3</td>
</tr>
<tr>
<td>2.</td>
<td>205</td>
<td>=<strong>C</strong>Br</td>
<td>207</td>
<td>68% and 3:1</td>
</tr>
<tr>
<td>3.</td>
<td>205</td>
<td>=<strong>S</strong>ZnBr</td>
<td>208</td>
<td>70% and 7:3</td>
</tr>
<tr>
<td>4.</td>
<td>205</td>
<td>=<strong>S</strong>Al(k-Bu)</td>
<td>209</td>
<td>60% and 2.5:1</td>
</tr>
</tbody>
</table>

c) Isolated yield.

d) Determined from crude $^1$H NMR spectrum.
The generality of the reaction was tested on sulfide \textbf{211} obtained by a initial alkylation of the thiol \textbf{202} with the silyl ether of 2-chloro ethanol followed by benzoylation, Scheme 61. The structure of \textbf{211} was confirmed by its $^1$H NMR spectrum which showed peaks at $\delta$ 5.14-5.11 (m) for -CH-OBz, 3.63 (t) for -CH$_2$OTBS and 2.66 (t) for -SCH$_2$ and peaks at 0.93 (s), 0.05 (s) and 0.04 (s) for the t-butyl and methyl groups respectively of the silyl ether.

\textbf{Scheme 61.}

The chlorosulfide prepared from \textbf{211} reacted with vinylzinc bromide to yield sulfide \textbf{213} in 68\% yield and 3:1 dr. The identity of the compound \textbf{213} was confirmed by its $^1$H NMR spectrum which revealed peaks at $\delta$ 5.82 (m) for internal olefinic proton 5.34-5.04 (m, 3H) for the terminal olefinic protons and -CHOBz, 3.48-3.45 (m) for -CHS-. The reaction attempted with octynyliczinc bromide also delivered the product \textbf{214} as a mixture of diastereoisomers in a 7:3 ratio, Scheme 62.

\textbf{Scheme 62.}

\textbf{6. Conclusion}

To obtain chiral substituted sulfides using chiral catalysts and chiral auxiliaries plenty of efforts were taken. Using chiral catalysts we could not achieve good yield and selectivity. To improve the selectivity, reactions were carried out in different solvents and at different temperatures but in vain. The chiral camphor based chiral auxiliary was employed to secure a chiral sulfide. The desired product was obtained in good yield but with poor selectivity along with regioisomer in C3 position. To avoid C3 chlorination, it was planned to substitute the C3
Experimental section:

**Compound 182:** (Carriera protocol) Zn(OTf)\(_2\) (36 mg, 0.10 mmol) in a 10 mL flask was flame dried under high vacuum (< 0.5 mm/Hg). The flask was cooled to rt and (+)-N-methylephedrine (20 mg, 0.11 mmol) was added. To this mixture was added anhydrous CH\(_2\)Cl\(_2\) (1 mL) and triethylamine (25 mg, 0.25 mmol). The resulting mixture was stirred for 2 h at rt before a solution of corresponding alkyne (0.60 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added in one portion. After stirring for 30 min a solution of chlorosulfide 146 (0.50 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added. The reaction mixture was stirred for 7 h. The reaction was quenched by addition of saturated aq NH\(_4\)Cl. The reaction mixture was poured into a separatory funnel containing diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude compound was purified by column chromatography using hexanes/EtOAc (98:2, v/v) to afford 182 (33 mg, 0.1 mmol) in 20 % yield as a liquid. TLC R\(_f\) = 0.30 (4% EtOAc/Hexanes). \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.52-7.03 (m, 10H), 3.82-3.64 (m, 1H), 2.98-2.63 (m, 2H), 2.31-2.13 (m, 2H), 2.11-1.91 (m, 2H), 1.56-1.06 (m, 8H), 0.94 (t, J = 6.8 Hz, 3H). Compound 183 and 184 were prepared following the procedure detailed for the preparation of 182. Compound 183: yield 24% (50 mg, 0.12 mmol), enantiomer ratio 58:42, TLC R\(_f\) = 0.24 (4% EtOAc/Hexanes). \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.49-7.11 (m, 10H), 4.33 (s, 2H), 3.73 (t, J = 6.1 Hz, 1H), 2.96-2.72 (m, 2H), 2.09-1.99 (m, 2H), 0.93 (s, 9H), 0.05 (s, 6H). **Compound 184:** yield 42% (68 mg, 0.21 mmol), enantiomer ratio 6:4, TLC R\(_f\) =
0.28 (4% EtOAc/Hexanes). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.58-7.13 (m, 15H), 3.92 (t, \(J = 6.1\) Hz, 1H), 3.02-2.81 (m, 2H), 2.20-2.08 (m, 2H).

**Compound 184:** (using Pu’s protocol): A solution of phenyl acetylene (0.26 mL, 2 mmol) and diethyl zinc (1 mL, 2 M in hexane, 2 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was stirred for 2 h under nitrogen. A solution of (S)-BINOL (57.2 mg, 0.2 mmol) in CH\(_2\)Cl\(_2\) (2 mL) and Ti(OiPr)\(_4\) (0.15 mL, 0.5 mmol) were added sequentially. The solution was stirred for another hour and chlorosulfide 146 (0.5 mmol) was added. After additional 7 h, the reaction was quenched with saturated NH\(_4\)Cl. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and evaporated to afford crude product. The crude compound was purified by column chromatography using hexanes/EtOAc (98:2, v/v) to afford product 184 (81 mg, 0.21 mmol) in 42% yield as a liquid and diastereomeric ratio was found to be 62:38.

**Compound 191:** To a solution of iPr\(_2\)NH (1.65 mL, 12 mmol) in anhydrous THF (20 mL) cooled at 0 °C was added n-butyllithium (4.8 mL, 2.5M in hexane, 12 mmol) and stirred for 20 min. The reaction mixture was cooled to -78 °C and a solution of (+)-camphor 189 (1.5 g, 10 mmol) in THF (10 mL) was added. The solution was stirred for 1.5 h and added via a cannula to a solution of the benzyl thiosylate 190 (2.7 g, 12 mmol) in a mixture of HMPA (5.4 mL, 30 mmol) and THF (10 mL) at -78 °C. The resulting mixture was stirred at this temperature for 2 h. It was quenched at -78 °C with saturated aqueous sodium hydrogen sulfate and extracted with ether (3×30 mL). The combined ether extracts were washed with 1N hydrochloric acid and saturated aqueous sodium hydrogen carbonate, dried over Na\(_2\)SO\(_4\) and the solvent evaporated. The crude product was purified by chromatography using hexanes/EtOAc (95:5, v/v) to afford the product 191 (2 g, 7.4 mmol) in 74% yield as a oil. TLC \(R_f = 0.12\) (10% EtOAc/Hexanes). \(^1\)H NMR \(\delta\) 7.37-7.22 (m, 5H), 4.01 (d, \(J = 9.7\) Hz, 1H), 3.93 (d, \(J = 9.7\) Hz, 1H), 2.74 (s, 1H), 1.93-1.84 (m, 2H), 1.60-1.41 (m, 2H), 1.23 (m, 1H), 0.98 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H).
**Compound 192**: To a solution of compound 191 (1.34 mg, 5 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) cooled at 0 °C was added DIBAL-H (4 mL, 1.5 M in toluene, 6 mmol) dropwise and stirred for 30 min. The reaction mixture was quenched by addition of saturated NH$_4$Cl solution and extracted into ether (3×40 mL). The combined extracts were washed with 1N hydrochloric acid, saturated sodium hydrogen carbonate solution, dried over anhydrous Na$_2$SO$_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography with hexanes/EtOAc (9:1, v/v) to furnish product 192 (1.08 g, 4.05 mmol) in 81% yield as a colorless oil. TLC $R_f$ = 0.10 (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.31-7.26 (m, 5H), 3.66 (s, 2H), 3.40 (d, $J$ = 7.5 Hz, 1H), 2.86 (d, $J$ = 7.5 Hz, 1H), 1.78-1.67 (m, 2H), 1.47-1.39 (m, 2H), 1.05-0.96 (m, 4H), 0.91 (s, 3H), 0.75 (s, 3H).

**Compound 193**: To a solution of 192 (1.07 g, 4.0 mmol) in anhydrous CH$_2$Cl$_2$ (12 mL) cooled at 0 °C was added Et$_3$N (0.84 mL, 6 mmol), followed by benzoyl chloride (510 mL, 4.8 mmol) and the mixture stirred for 3 h at ambient temperature. The reaction mixture was diluted water, the layer separated and the aq layer extracted with dichloromethane (2×25 mL). The combined organic layer were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to afford a crude product which was purified by column chromatography using hexanes/EtOAc (9:1, v/v) as the eluent to afford product 193 (1.4 g, 3.76 mmol) in 94% yield as a viscous oil. TLC $R_f$ = 0.16 (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): δ 8.16-8.08 (d, $J$ = 6.8 Hz, 2H), 7.58-7.41 (m, 3H), 7.34-7.11 (m, 5H), 5.08 (d, $J$ = 7.1 Hz, 1H), 3.62 (s, 2H), 2.90 (d, $J$ = 7.1 Hz, 1H), 1.81-1.66 (m, 2H), 1.62-1.47 (m, 2H), 1.31-1.21 (m, 4H), 0.88 (s, 3H), 0.81 (s, 3H).

**General procedure for chlorosulfide reaction**: Compound 194 and 195: To a solution of sulfide 193 (186 mg, 0.5 mmol) in anhydrous benzene (5 mL) was added NCS (77 mg, 0.55 mmol) and stirred for 1 h. The TLC examination revealed complete conversion of starting sulfide. In another RB flask containing Vinylmagnesium bromide (1.4 mL, 0.7 M in THF, 1.0 mmol) cooled at 0 °C was added ZnBr$_2$ (0.66 mL, 1.5 M in THF, 1.0 mmol) and the mixture...
stirred for 30 min. The chlorosulfide was added slowly to the vinylzinc bromide solution and stirred further for 7 h. The reaction mixture was quenched by the addition of aq saturated NH₄Cl and diluted with ether. The layers were separated and the aq layer was extracted with ether (2×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and the solvent evaporated to afford a crude product that was purified by column chromatography using hexanes/EtOAc (9:1, v/v) as the eluent to afford an inseparable mixture (1:1 ratio) of 194 and 195 (135 mg, 0.34 mmol) in 68% yield as a viscous oil. Diastereomer ratio of 194 was 3:1.

**Compound 194:** TLC Rf = 0.15 (10% EtOAc/hexanes). ¹H NMR (300 MHz, CDCl₃): δ 8.16-8.08 (d, J = 6.4 Hz, 4H), 7.63-7.03 (m, 16H), 5.79 (m, 2H), 5.33-4.86 (m, 6H), 4.31 (d, J = 8.3 Hz, 1H), 3.32 (d, J = 7.8 Hz, 1H), 2.86-2.74 (m, 2H), 2.04-1.08 (m, 16H), 1.02-0.71 (m, 12H).

**Compound 195:** TLC Rf = 0.15 (10% EtOAc/hexanes). ¹H NMR (300 MHz, CDCl₃): δ 8.16-8.08 (d, J = 6.4 Hz, 2H), 7.63-7.03 (m, 8H), 6.19 (dd, J = 10.0, 5.6 Hz, 1H), 5.33-4.86 (m, 3H), 3.61 (s, 2H), 2.04-1.08 (m, 8H), 1.02-0.71 (m, 6H).

**Compound 196:** To a solution of iPr₂NH (1.65 mL, 12 mmol) in anhydrous THF (20 mL) cooled at 0 °C was added n-BuLi (4.8 mL, 2.5M in hexane, 12 mmol) and stirred for 20 min. The reaction mixture was cooled to -78 °C and a solution of (+)-camphor 189 (1.5 g, 10 mmol) in THF (10 mL) was added. The solution was stirred for 1.5 h and a solution of the methyl iodide (1.25 mL, 20 mmol) in a mixture of HMPA (3.6 mL, 20 mmol) and THF (10 mL) was added at -78 °C. The resulting mixture was stirred at this temperature for 2 h. It was quenched at -78 °C with saturated aqueous NaHSO₄ and extracted with ether (3×30 mL). The combined ether extracts were washed successively with 1N hydrochloric acid, saturated aqueous NaHCO₃, dried over Na₂SO₄ and the solvent evaporated. The crude product was purified by chromatography using hexanes/EtOAc (95:5, v/v) to afford the product 196 (1.34 g, 8.1 mmol) in 81% yield as an oil. TLC Rf = 0.12 (10% EtOAc/hexanes). ¹H NMR δ 2.52-2.38 (m, 1H), 2.04-1.79 (m, 4H), 1.62-1.34 (m, 4H), 1.16 (d, J = 7.2 Hz, 3H), 0.94 (s, 3H), 0.89 (s, 3H).
**Compound 197**: Obtained following the same procedure detailed for the preparation of compound 191. The product was obtained in 74% yield and as a 7:3 ratio of isomers. The isomers were separated by column chromatography. **For major isomer**: TLC $R_f = 0.12$ (10% EtOAc/hexanes). $^1$H NMR $\delta$ 7.45-7.14 (m, 5H), 4.08 (d, $J = 6.4$ Hz, 1H), 4.01 (d, $J = 6.4$ Hz, 1H), 2.02-1.63 (m, 3H), 1.52 (s, 3H), 1.47-1.38 (m, 2H), 1.26 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H).

**Compound 198**: Prepared from 197 by reduction using DIBAL-H as described for compound 192. The product 198 was obtained in 81% yield as an inseparable mixture of exo and endo isomers in almost equal ratio. TLC $R_f = 0.10$ (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.41-7.21 (m, 10H), 3.82 (s, 2H), 3.61 (s, 1H) 3.52 (s, 2H), 3.12 (s, 1H), 1.78-1.51 (m, 12H), 1.49-1.37 (m, 4H), 1.28 (s, 6H), 0.92 (s, 6H), 0.87 (s, 6H).

**Compound 201**: To a solution of (+)-pulegone 200 (1.52 g, 10 mmol) in anhydrous toluene (30 mL) was added DBU (0.37 mL, 2.5 mmol) followed by benzyl mercaptan (1.3 mL, 11 mmol) and the mixture stirred for 7 h. The reaction mixture was diluted with ether and water. The layers were separated and the aq layer was extracted with ether (2×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and the solvent evaporated. The crude product was purified by chromatography using hexanes/EtOAc (90:10, v/v) to afford the product 201 (2.04 g, 7.8 mmol) in 78% yield as a oil. TLC $R_f$ = 0.10 (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.29-7.21 (m, 5H), 3.71 (apparent d, $J = 7.5$ Hz, 2H), 2.69 (dt, $J = 15.3$, 4.0 Hz, 1H), 2.50 (dd, $J = 11.0$, 2.1 Hz, 1H), 2.30-2.19 (m, 1H), 1.99-1.92 (m, 5H), 1.90-1.83 (m, 1H), 1.77 (s, 3H), 1.64-1.57 (m, 1H), 1.39-1.26 (m, 1H), 1.01 (d, $J = 6.0$ Hz, 3H).
Compound 202: A solution of 201 (1.57 g, 5 mmol) in methanol (10 mL) was added to a mixture of lithium (350 mg, 50 mmol) in liquid ammonia (10 mL) at -78 °C slowly. The reaction was stirred for 4 h and quenched with aq saturated NH₄Cl and diluted with ether. After attaining rt, the layers were separated and the aq layer was extracted with ether (4×30 mL), the combined organic layer were washed with brine, dried over anhydrous Na₂SO₄. The solution was evaporated and the crude product was purified by chromatography using hexanes/EtOAc (90:10, v/v) to afford the product 202 (651 mg, 3.5 mmol) in 70% yield as a oil. TLC Rᶠ = 0.10 (10% EtOAc/hexanes). ¹H NMR (300 MHz, CDCl₃): δ 3.67 (td, J = 10.2, 4.0 Hz, 1H), 2.09-2.00 (m, 2H), 1.97-2.00 (m, 2H), 1.69-1.62 (m, 3H), 1.50 (s, 3H), 1.47-1.37 (m, 4H), 0.90 (d, J = 6.4 Hz, 3H).

Compound 203: To a solution of hydroxy thiol 202 (750 mg, 4 mmol) in anhydrous THF (12 mL) was added Et₃N (0.83 mL, 6 mmol) followed by benzyl chloride (0.55 mL, 4.8 mmol) and the mixture stirred for 4 h at rt. The reaction mixture was transferred to a separatory funnel containing water. The layers were separated and the aqueous layer was extracted with ether (2×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, the solvent evaporated and the crude residue was purified by column chromatography using hexanes/EtOAc (9:1, v/v) as the eluent to afford product 203 (950 mg, 3.24 mmol) in 81% yield as a viscous oil. TLC Rᶠ = 0.16 (10% EtOAc/hexanes). ¹H NMR (300 MHz, CDCl₃): δ 7.32-7.18 (m, 5H), 3.90 (d, J = 11.2 Hz, 1H), 3.73 (d, J = 11.2 Hz, 1H), 3.67 (td, J = 9.8, 3.8 Hz, 1H), 1.97-1.61 (m, 4H), 1.41-1.34 (m, 8H), 1.28-1.23 (m, 2H), 0.85 (d, J = 6.2 Hz, 3H).

Compound 204: Prepared following the same procedure used for preparing 193. Compound 203 (880 mg, 3.0 mmol) afforded product 204 (1.4 g, 3.76 mmol) in 94% yield as a viscous oil. TLC
$R_f = 0.16$ (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.01 (d, $J = 7.8$ Hz, 2H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.41 (t, $J = 7.8$ Hz, 2H), 7.29-7.14 (m, 5H), 5.60-5.56 (m, 1H), 3.66 (s, 2H), 2.06-2.00 (m, 2H), 1.84-1.76 (m, 3H), 1.50-1.46 (m, 1H), 1.41-1.32 (m, 4H), 1.26 (s, 3H), 1.03-0.96 (m, 1H), 0.83 (d, $J = 5.8$ Hz, 3H).

**Compound 206, 207, 208 and 209:** Following the general procedure, reaction of chlorosulfide obtained from 204 (186 mg, 0.5 mmol) with vinylzinc bromide afforded an inseparable mixture of diastereomers of 206 (125 mg, 0.32 mmol) in a 7:3 dr in 64% yield as a liquid. TLC $R_f = 0.15$ (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.00-8.01 (m, 4H), 7.55-7.38 (m, 6H), 7.34-7.17 (m, 10H), 6.12-6.02 (m, 2H), 5.13-4.98 (m, 6H), 4.57-4.53 (m, 2H), 2.40-1.88 (m, 8H), 1.79-1.45 (m, 6H), 1.43 (s, 6H), 1.29-1.24 (m, 8H), 0.92 (d, $J = 6.6$ Hz, 6H). Compound 207: Following the general procedure, 2-methyl propenylzinc bromide reacted with chlorosulfide 205 to furnish the product 207 in 68% yield and 3:1 diasteromer ratio. TLC $R_f = 0.15$ (10% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.00-7.91 (m, 4H), 7.47-7.30 (m, 6H), 7.27-7.09 (m, 10H), 5.34 (d, $J = 10.7$ Hz, 1H) (for major isomer), 5.26 (d, $J = 10.7$ Hz, 1H) (for minor isomer), 5.08-4.93 (m, 2H), 4.67 (d, $J = 10.7$ Hz, 2H), 2.35-2.30 (m, 2H), 2.17-1.78 (m, 12H), 1.71-1.43 (m, 18H), 1.34 (s, 6H), 1.23-1.13 (m, 2H), 0.85 (d, $J = 6.4$ Hz, 3H) (for major isomer), 0.78 (d, $J = 6.4$ Hz, 3H) (for minor isomer). Compound 208: Following the general procedure octynylzinc bromide afforded product 208 in 70% yield and as a 7:3 mixture of diastereomers. TLC $R_f = 0.15$ (11% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.00-7.91 (m, 4H), 7.47-7.30 (m, 6H), 7.27-7.09 (m, 10H), 4.98-4.91 (m, 2H), 4.60-4.58 (m, 2H), 2.28-2.04 (m, 4H), 1.74-1.52 (m, 12H), 1.50-1.02 (m, 32H), 0.99-0.74 (m, 12H). Compound 209: Following the general procedure E-octenyl alane provided product 209 in 60% yield and in a diasteromer ratio 2.5:1. TLC $R_f = 0.15$ (11% EtOAc/Hexanes). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.02-7.92 (m, 4H), 7.49-7.21 (m, 16H), 5.78-5.39 (m, 4H), 4.72-4.68 (m, 2H), 3.64-3.51 (m, 2H), 2.04-1.81 (m, 4H), 1.77-1.49 (m, 6H), 1.47-1.08 (m, 38H), 0.94-0.73 (m, 12H).
**Compound 211:** Obtained from 202, following a route identical to that detailed for the preparation of compound 204 from 202. Yield 68% overall for two steps. TLC R_f = 0.13 (10% EtOAc/hexanes). ^1^H NMR (300 MHz, CDCl_3): δ 8.11-8.01 (m, 2H), 7.56-7.41 (m, 3H), 5.17-5.09 (m, 1H), 3.66-3.59 (m, 2H), 2.68-2.52 (m, 2H), 2.18-2.12 (m, 1H), 1.87-1.71 (m, 2H), 1.62-1.53 (m, 1H), 1.48-1.39 (m, 5H), 1.37-1.25 (m, 5H), 0.97-0.90 (m, 12H), 0.04 (s, 6H). ^13^C NMR (75 MHz, CDCl_3): 165.5, 132.7, 130.8, 129.6, 128.2, 74.6, 63.2, 49.7, 41.7, 34.4, 31.2, 30.5, 30.3, 27.4, 26.4, 25.9, 25.6, 21.6, 18.3, -5.3.

**Compound 213:** Following the general procedure sulfide 211 afforded an inseparable mixture of diasteromers of compound 213 in a 3:1 ratio in 68% yield. TLC R_f = 0.12 (10% EtOAc/hexanes). ^1^H NMR (300 MHz, CDCl_3): δ 8.14 (d, J = 7.2 Hz, 4H), 7.55 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 4H), 5.86-5.73 (m, 2H), 5.21-5.02 (m, 6H), 3.72-3.68 (m, 2H), 3.50 (dd, J = 15.3, 9.8 Hz, 2H), 3.38-3.31 (m, 2H), 2.40-2.30 (m, 2H), 2.16-2.08 (m, 2H), 1.94-1.81 (m, 2H), 1.77-1.68 (m, 4H), 1.65-1.53 (m, 2H), 1.44 (s, 6H), 1.32-1.22 (m, 10H), 1.02-0.87 (m, 24H), 0.02 (s, 12H). MS (ESI) 494 [M+NH_4]^+. 

**Compound 214:** Following the general procedure sulfide chlorosulfide obtained from 211 on reaction with octynylzinc bromide afforded an inseparable mixture of diastereomer of 214 in a 7:3 ratio in 68% yield. TLC R_f = 0.13 (10% EtOAc/hexanes). ^1^H NMR (300 MHz, CDCl_3): δ 8.17-8.08 (m, 4H), 7.57-7.52 (m, 2H), 7.48-7.41 (m, 4H), 5.18-5.12 (m, 2H), 3.68-3.59 (m, 4H), 3.54-3.47 (m, 2H), 2.72-2.52 (m, 2H), 2.41-2.01 (m, 6H) 1.97-1.84 (m, 6H), 1.79-1.18 (m, 34H), 1.02-0.79 (m, 30H), 0.04 (s, 12H).
References:

SPECTRA
$^1$H NMR spectrum of Compound 140
$^{13}$C NMR spectrum of Compound 140
$^1$H spectrum of Compound 148
$^{13}$C NMR spectrum of Compound 148
$^1$H NMR spectrum of Compound 149
$^{13}$C NMR spectrum of Compound 149
$^1$H spectrum of Compound 150
$^{13}$C NMR spectrum of Compound 150
$^1$H spectrum of Compound 157

![Chemical structure of Compound 157 with corresponding NMR spectrum]
$^{13}$C NMR spectrum of Compound 157
$^1$H spectrum of Compound 162
\(^{13}\)C NMR spectrum of Compound 162
$^1H$ spectrum of crude Compound 165 and 166
$^1\text{H}$ spectrum of Compound 174
\(^{13}\)C NMR spectrum of Compound 174
$^1\text{H}$ spectrum of Compound 176
$^{13}$C NMR spectrum of Compound 176
Crude spectrums

$^1$H spectrum of Compound 148

$^1$H spectrum of Compound 149
Section II

$^1$H spectrum of Compound 183
HPLC spectrum of Racemic Compound 184
HPLC spectrum of Compound 184 (obtained by Carreira protocol)
$^1$H spectrum of Compound 193
$^1$H spectrum of mixture of Compound 194 and 195
\(^1\text{H} \text{ spectrum of Compound 204} \)
$^1$H spectrum of Compound 207

![H spectrum of Compound 207]
$^1$H spectrum of Compound 211

![Spectrum Image]
$^1$H spectrum of Compound 213