GENERALIZATION OF HIGHLY γ-REGIOSELECTIVE SUBSTITUTIONS IN ALLYL HALIDES BY ALKYLZINCS AND APPLICATIONS TO ZINC-ENE CYCLIZATIONS AND THE SYNTHESIS OF (*R*)-(+)-DIHYDRO-α-IONONE.

by

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MS, Moscow State University, 1999

Submitted to the Graduate Faculty of

University of Pittsburgh in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

CHEMISTRY DEPARTMENT

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February 25, 2008

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GENERALIZATION OF HIGHLY γ-REGIOSELECTIVE SUBSTITUTIONS IN ALLYL HALIDES BY ALKYLZINCS AND APPLICATIONS TO ZINC-ENE CYCLIZATIONS AND THE SYNTHESIS OF (*R*)-(+)-DIHYDRO-α-IONONE.

Roman A. Ivanov, Ph. D.

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Allyl phenyl sulfides have proven to be extremely versatile and widely used reagents in organic chemistry. There are thousands of publications that relate their uses in synthesis. However, the conventional method of preparing γ-substituted allyl phenyl sulfides by alkylation of deprotonated commercially available allyl phenyl sulfides, only allows electrophilic groups to be introduced. This method fails if the alkylating agent is tertiary, secondary, vinylic, or arylic. In this work a new method, in which a nucleophilic group can be introduced at the carbon atom bearing the phenylthio group, referred to as γ-allylic substitution, is thoroughly studied and used in several examples to demonstrate its significance for synthesis. This procedure should vastly increase access to a wide variety of allyl phenyl sulfides. In this work, copper mediated γ-allylic substitution reactions of organozinc reagents with allyl chlorides bearing a γ-phenylthio group are reported and the best reaction conditions for mono- and dialkylzincs are revealed. The scope and limitations of γ-allylic substitutions of organozincs with a variety of different allyl chlorides were thoroughly investigated and an important temperature effect was observed and used to expand the scope of these reactions.

Furthermore, this work deals with an important aspect of the preparation of the organometallic nucleophiles required for these γ-substitutions. Many of these can be prepared by reductive lithiation of readily available alkyl phenyl thioethers by aromatic radical-anions. However, large-scale preparations suffer from the requirement of separation of the desired product from the aromatic byproduct using either slow column chromatography or vacuum sublimation. An improved procedure for reductive lithiation of phenyl thioethers with 1-(*N*,*N*-dimethylamino)naphthalenide was developed to overcome this drawback. Reductive lithiation was then used not only as a preliminary step in the preparation of organozincs for copper mediated γ-regioselective substitution reactions but also as a key step in the enantioselective synthesis of (*R*)-(+)-dihydro-α-ionone.

It was demonstrated that the combination of reductive lithiations, zinc-ene reactions and copper mediated organozinc γ-regioselective substitutions can be used for efficient syntheses of ring-fused intermediates in an iterative and stereoselective fashion from inexpensive commercially available starting compounds.

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PREFACE

The five years that I have spent here have amounted to a fantastic experience; I have many people to thank for that. First and foremost, I want to thank my advisor Ted Cohen with my deepest gratitude. He guided me into the wonderful area of intramolecular carbometallation. He was always there to help when I had difficulties in experiments. Especially, he encouraged me to pursue my own ideas in the research. Besides his comprehensive knowledge in chemistry, his zeal for science and his healthy life style also impress me.

I would also like to thank Professors Peter Wipf, Craig Wilcox and Michael Mokotoff for serving on my thesis committee and Professors Kay Brummond, Toby Chapman and Stephane Petoud for being on the committee for my proposal defense. Their willingness to share their expertise and provide valuable advice is greatly appreciated.

I am very grateful for the help provided by Dr. Damodaran Krishnan and Dr. John Williams in NMR spectroscopy and mass spectrometry, respectively.

A large part of my graduate experience has been interacting with the great people in the Cohen group, past and present. I want to thank them for their help and friendship. I had the privilege to talk with Jeananne Singletary and Justin Chalker on many chemistry problems. Adam Robb and Sam Lemonick worked with me on several experiments. I enjoyed working with them and want to thank them all. Especially I want to thank Adam Robb, who made very valuable contributions in this work and Justin Chalker, who gave me some valuable advice.

Last but not the least, I want to thank my wife Madina R. Akhmetshina, whose constant love and understanding has supported me during the past five years, and both of my very close friends Dmitri Pavlov (Moscow State University, Russia) and Yuri Zimenkov (TransForm Pharmaceuticals, Inc USA). My special thanks also go to my parents and grandparents, who made me the person I am now.

LIST OF ABBREVIATIONS

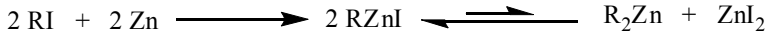
Ac	acetyl	*m*CPBA	3-chloroperoxybenzoic acid
Alk	alkyl	Ms	mesylate
9-BBN	9-borabicyclo[3.3.1]nonane	MVK	methyl vinyl ketone
Bn	benzyl	NCS	*N*-chlorosuccinimide
Boc	benzyloxycarbonyl	NMP	N-methyl-pyrrolidone
DBB	4,4'-*t*-butylbiphenyl	NMR	nuclear magnetic resonance
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	Nu	nucleophile
DCM	dichloromethane	PDC	pyridinium dichromate
Dibal-H	diisobutylaluminum hydride	Pyr	pyridine
DMAN	1-(dimethylamino)naphthalene	TBAF	tetra-*n*-butylammonium fluoride
DMAP	4-dimethylaminopyridine	TEA	triethylamine
dppf	1,1'-*bis*(diphenylphosphino)ferrocene	Tf	triflate
GC	gas chromatography	TFA	trifluoroacetic acid
HMPA	hexamethylphosphoramide	THF	tetrahydrofuran
Me-Im	methyl imidazole	TLC	thin layer chromatography
KHMDS	potassium *bis*(trimethylsilyl)amide	TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
LAH	lithium aluminum hydride	TMS	trimethylsilyl
LDBB	lithium 4,4'-di-*tert*-butylbiphenylide	Ts	tosylate
LDMAN	lithium 1-(dimethylamino)naphthalenide		
LN	lithium naphthalenide		

1.0 ALKYLZINC REAGENTS IN γ-ALLYLIC SUBSTITUTION REACTIONS MEDIATED BY COPPER (I) CATALYSTS

1.1 INTRODUCTION

1.1.1 Organozinc Reagents

Organozinc reagents were discovered in 1849 by heating a mixture of zinc metal and methyl iodide.[1] The reaction, which involves a Schlenk-type equilibrium (Scheme 1.1), is still commonly used with some minor variations to prepare monoalkylzinc reagents as well as dialkylzincs.[2]

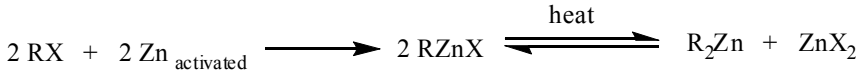


Scheme 1.1. Preparation of organozinc reagents and Schlenk equilibrium

Many aspects of the basic reactivity of organozincs were reported before the end of the nineteenth century, resulting in the discovery of the Reformatsky reaction, the conversion of α-bromoesters into zincated esters, in 1887.[3] However, the discovery of other classes of organometallic reagents, especially Grignard reagents, put an end to that first period of

organozinc chemistry. With extremely low basicity, in comparison with even Grignard reagents, the major problem of organozinc chemistry was the low nucleophilicity, leading to moderate reactivity. Nevertheless, this very drawback became the grounds for the revival of organozinc reagents. Since it was possible to prepare organozincs bearing a large range of different functional groups, in particular, electrophilic ones such as carbonyls, it was realized that organozincs could be very useful since they undergo smooth transmetallation to give a broad range of organometallics. Thus, their synthetic applications have greatly increased.[4]

The preparation of ordinary alkylzinc reagents by oxidative zincation, as given in Scheme 1.2, is rather limited by the fact that only certain leaving groups (X: I, Br, OSO_2R, $OP(O)(OR)_2$) are successfully replaced by zinc.[5]



Scheme 1.2. Preparation of ordinary organozincs by oxidative zincation (X = I, Br, OSO_2R, $OP(O)(OR)_2$.

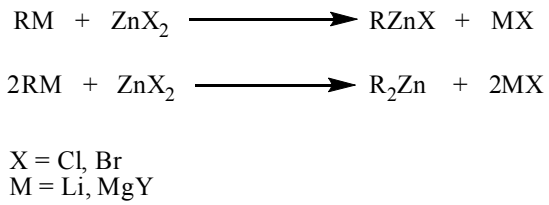
Zinc dust, activated according to Knochel's procedure, with TMSCl and 1,2-dibromoethane, reacts with primary and secondary iodides in THF at 25 to 40 °C in 0.5 to 3 h.[6] Primary alkyl tosylates, mesylates and phosphates have also been converted into the corresponding organozincs in DMA or DMPU at 50 – 60 °C in 6 – 12 h in the presence of a catalytic amount of LiI.[7]

The use of a special reactive form of zinc metal, such as Rieke® zinc,[8] allows the inclusion of alkyl bromides, which are usually unreactive toward zinc. Alkyl, cycloalkyl and homobenzylic bromides and iodides react with Rieke zinc prepared by reduction of zinc halides

with lithium naphthalenide and give excellent yields after reaction for 3 to 6 h in THF at room temperature.[2b] The formation of organozincs from secondary and *tert*-alkyl bromides can be also accomplished by using Rieke® zinc in THF at ambient or reflux temperature.[9]

Allylic bromides can be easily converted into the corresponding organozincs in medium to high yields in THF or DME. Even allyl chlorides can be converted into the corresponding organozincs in DMSO[10] at 5 to 25 °C using zinc dust activated according to Knochel.[11] However, allyl iodides and substituted allyl bromides are subject to Wurtz coupling.

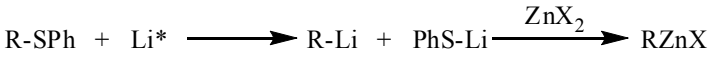
The transmetallation reaction of organolithiums[12] and Grignard reagents[13] with zinc halides has proven to be the most synthetically useful methods for the preparation of organozinc reagents (Scheme 1.3). Unfunctionalized and many functionalized organolithiums can be easily prepared by reductive lithiation and halogen-lithium exchange, while their transmetallation allows an easy access to organozinc reagents that cannot be prepared by oxidative zincation.



Scheme 1.3. Transmetallation reactions with zinc halides.

Organozinc halides and diorganozinc reagents can be prepared by the reaction of lithium and magnesium organics with zinc halides in a 1:1 or 2:1 molar ratio in THF or in ether at low temperature.[14] For transmetallation, a solution of commercially available anhydrous $ZnCl_2$ or flame-dried $ZnBr_2$ in THF is used.

The use of transmetallation expands the number of organic substrates RX that might be used as precursors for organozinc reagents RM and allows the inclusion of phenyl thioethers as a preferred source of carbanions (Scheme 1.4).[15]



Scheme 1.4. Thioethers as precursors for organozinc reagents.

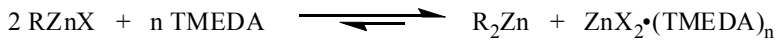
Due to the presence in RZnX of an electronegative group (X) directly bound to zinc, the Lewis acidity of the zinc atom in monoorganozinc compounds is enhanced and they readily form complexes with donor molecules in which the zinc atom has tetrahedral geometry. A typical feature of such monoorganozincs is their tendency to form aggregates.[16] Aggregated structures occur as a result of the presence of heteroatoms that are bridging and act as multi-electron donors between zinc atoms.

A factor that always should be taken into account in the case of monoorganozinc reagents, especially in solutions, is the existence of the Schlenk equilibrium (Scheme 1.5).

Scheme 1.5. Schlenk equilibrium.

The equilibrium position depends on several factors: (i) the nature of the groups bound to zinc; (ii) the nature and polarity of the solvent; and (iii) the presence of additional donor molecules. For instance, TMEDA is known to strongly complex zinc halides.[17] This chelating

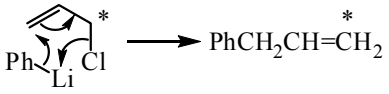
agent was found to be capable of shifting the Schlenk equilibrium (Fig 1.6)[17,18,19] to the right, thus increasing the concentration of the dialkylzinc.



Scheme 1.6. TMEDA facilitated Schlenk equilibrium.

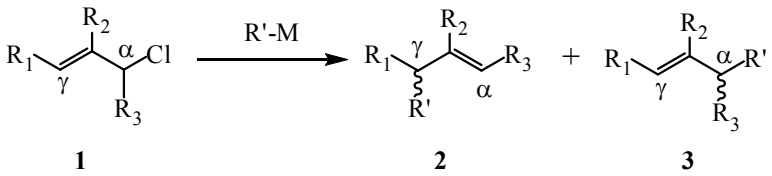
1.1.2 Copper-mediated Nucleophilic Substitution in Allylic Halides and Phosphate Esters at the γ-Allylic Carbon Atom (γ-S_{AL}) by Organometallics.

Alkylation of an organometallic reagent is an important carbon-carbon bond forming reaction, for which RLi and RMgX have generally been used as the source of the carbanionic moiety to be transferred to the alkylating reagent. Alkylation by allylic halides is usually a satisfactory reaction that may proceed through a cyclic mechanism.[20] For example, when [1-^{14}C] –allyl chloride reacts with phenyllithium, about 75% of the product has the labeled carbon at the terminal methylene group (Scheme 1.7). This type of product is called a γ-product and is formed by γ-displacement of the leaving group involving an allylic shift of the double bond.



Scheme 1.7. Alkylation by an allylic halide through a cyclic mechanism.

Unfortunately, reactions of an allylic chloride **1** (Scheme 1.8) with lithium or magnesium organometallics often lead to a mixture of γ-**2** and α-**3** substitution products. The latter is formed by direct displacement of the leaving group and is referred to as α-substitution (Scheme 1.8).[21]

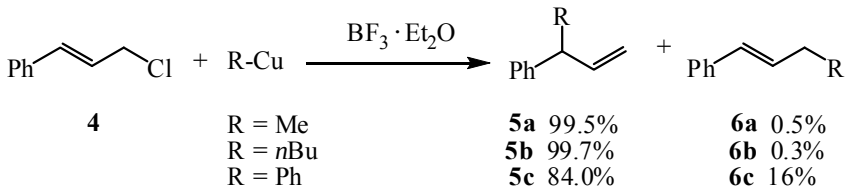


1 **2** **3**

Scheme 1.8. Regiochemistry of alkylation of allyl chlorides by organometallics.

The first example of a copper-mediated substitution reaction, between phenylcopper (PhCu) and allylic halides, was described by Gilman in 1936[22] followed by copper-mediated substitution reactions at saturated carbon reported in 1952, also by Gilman.[23] In the latter 1952 paper, Gilman reported the formation of lithium dimethylcuprate from polymeric methylcopper and methyllithium. These cuprates with general formula R_2CuLi were later called Gilman cuprates and used for substitution reactions on both saturated[24] and unsaturated substrates.

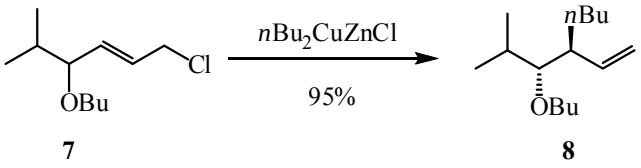
Subsequently, copper-mediated reactions of allylic halides with various types of organometallics were discovered to proceed smoothly with high yield and often with γ-regioselectivity. Yamamoto reported extremely high regioselectivity in alkylation of cinnamyl chloride **4** with a wide range of primary organocopper reagents in the presence of the Lewis acid BF_3[25] (Scheme 1.9).



Scheme 1.9. Reaction of cinnamyl chloride with various Yamamoto reagents.

However, there is not enough published information about whether alkyl groups more bulky than primary may be introduced γ-regioselectively using Yamamoto reagents.

Although Gilman lithium cuprates demonstrate poor γ-regioselectivity in allylic substitution reactions, it was discovered recently that conversion of a dialkyllithium cuprate to a zinc halocuprate provides a reagent that is remarkably γ-regioselective. For instance, in a reaction between dibutylzinc chlorocuprate and 4-alkoxy allylic chloride **7,** the product of only γ-attack, with the relationship between the two stereogenic centers predominantly of the *anti* configuration, **8** was observed (Scheme 1.10).[26]

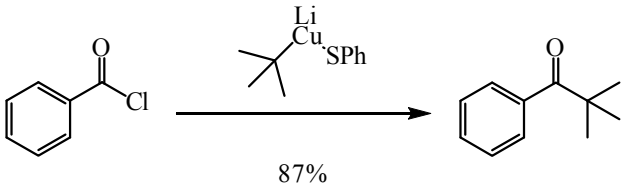


Scheme 1.10. γ-Regioselectivity of zinc halocuprates.

However, despite the extremely high regioselectivity toward γ-displacement, the use of dialkylzinc cuprates is limited by low thermal stability and by the fact that one of the two alkyl groups must be wasted in work-up as RH. Although tolerable for most commercially obtained

alkyllithiums, those cuprates whose precursors must be synthetically prepared and then lithiated are too costly to be sacrificed.

To avoid this drawback and to conserve all valued alkyl lithium reagent introduced into a reaction mixture, mixed ligand cuprates have been developed, which derive from two different organolithiums: one is the organometallic of interest, R_tLi (R_t = the transferable group); the other, R_dLi, consists of a "residual" or "dummy" ligand R_d which is less, if not at all, liable to be transferred from the copper. When R_tLi and R_dLi combine with CuX (X = I, Br), subsequent reaction with a suitable substrate leads to selective transfer of the R_t group in preference to R_d, with loss of the byproduct $(R_dCu)_n$ being of no chemical consequence. The alternative method to form a mixed cuprate is to combine R_tLi with stable, readily available copper reagents R_dCu, which possesses a "dummy" ligand at the very beginning. Many different "dummy" ligands (R_d) have been developed to be used mostly in the Michael addition (Scheme 1.11) or in acylation reactions: alkynic derivatives[27] such as lithiated *tert*-butylacetylene,[28] 2-thienyl,[29] dialkylphosphido,[30] cyano[31] (CN) and phenylthio[32] (SPh) groups.

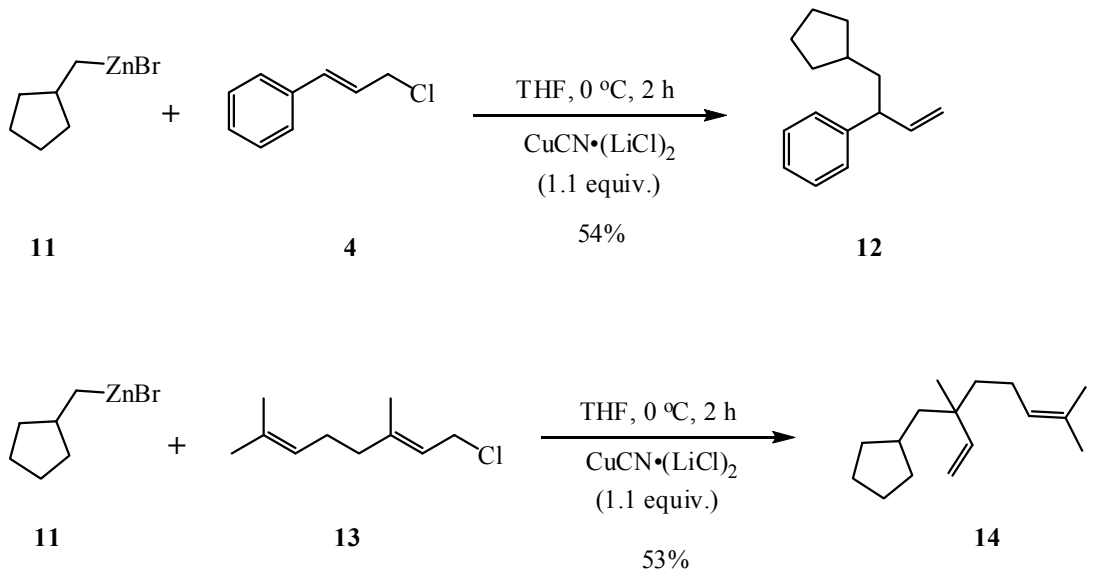


9 **10**

Scheme 1.11. SPh-group as a dummy ligand for Michael addition reactions.

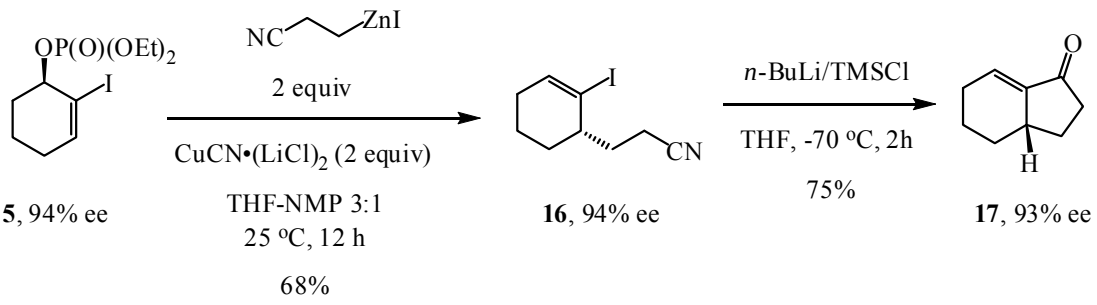
The cyano group has been the most thoroughly examined as a "dummy" ligand in the Michael addition as well as almost exclusively studied as a potential non-transferable group in

allylic substitution reactions with mixed organozinc-derived cuprates. Recently, Yus has reported the regioselective formation of γ-products in the alkylation of various allyl halides (Scheme 1.12) with low or moderate yields after 2 h at 0 °C.[33]



Scheme 1.12. Reaction of zinc cyanocuprates with allyl halides leading to γ-regioselective substitution with low or moderate yields.

Recently, Knochel reported an interesting enantioselective preparation of the bicyclic enone **17** using, as a key step, γ-regioselective alkylation of the alkyl phosphate **15** with 2 equiv of functionalized alkylzinc iodide and 2 equiv of CuCN (Scheme 1.13).[34]



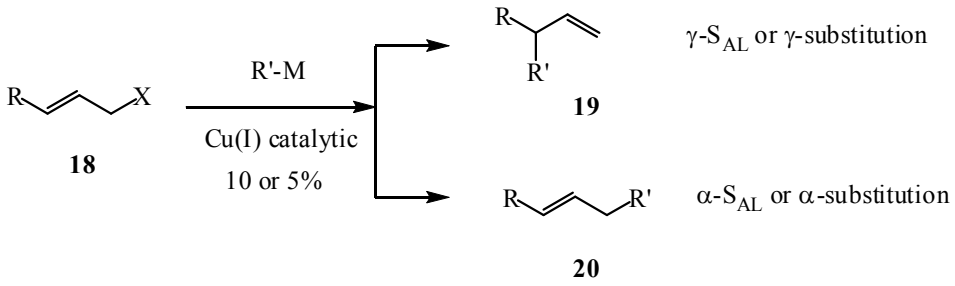
15, 94% ee **16**, 94% ee **17**, 93% ee

Scheme 1.13. Synthesis of the bicyclic enone **17** using γ-alkylation by an alkylzinc cyanocuprate as a key step.

From Scheme 1.13, it can be seen that not only a large amount (2 equiv) of very toxic CuCN and expensive dry LiCl (4 equiv) are used but also at least one equivalent of the alkylzinc iodide is wasted for no benefits. It should be noted that formation of a quantitative amount of a stoichiometric mixed cyanocuprate at such a high temperature (between 0 °C and room temperature) is doubtful.[35] It might be reasonable to assume formation of only a catalytic amount of the cyanocuprate that is very unstable under those conditions. All this clearly demonstrates how important it is to thoroughly investigate the γ-allylic substitution caused by organozincs and catalyzed by copper (I) salts in order to be able to find the optimum conditions for all types of substrates and organozinc reagents. Based on toxicity and stability in ambient conditions $CuBr•SMe_2$ should be considered as the catalyst of choice instead of highly toxic and hygroscopic CuCN•2LiCl

Taking into consideration the mechanistic aspect, the copper catalyzed allylic substitution reaction is fascinating since the substitution reaction can occur in two different ways with very high regioselectivity toward either direction depending on the organic substrate and other reaction parameters: α-displacement (**α-S_{AL}**) providing the product **20** and resembling an S_N2 process or/and a product **19**, expected of an S_N2' process and referred to here as **γ-S_{AL}** (Scheme

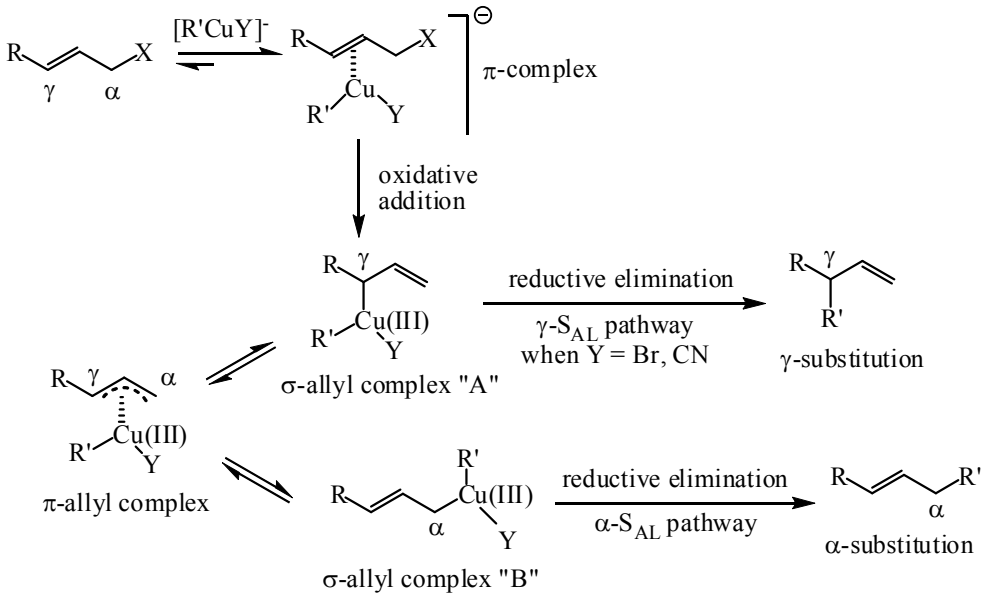
1.14). In certain cases of alkyl Grignard reagents, the regioselectivity can easily be switched between the two substitution modes by changing the reaction conditions.[36]



R = alkyl, aryl, allyl
M = Li, MgX, ZnX, etc
X = Cl, Br, OC(O)R", SO_2Ph, OR", $OP(O)(OR")_2$

Scheme 1.14. Copper-catalyzed allylic substitution.

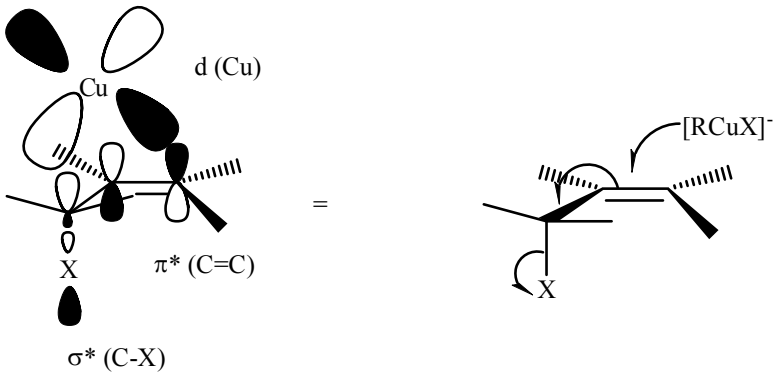
Mechanistically, these reactions are considered to start with formation of a metallocuprate in a small concentration followed by oxidative addition of the organocopper reagent to the allylic system to yield a $Cu^{(III)}$ intermediate or intermediates,[37,38] producing the final product by a reductive elimination as shown in Scheme 1.15. The oxidative addition is believed to be highly γ-selective, which would initially produce the σ-allyl complex **A,** and a fast reductive elimination from this complex, especially when **Y** is an electron-withdrawing group, would give the γ-product. It is believed that under slow reductive elimination conditions, especially when **Y** is an electron-donating group, the σ-allyl complex **A** would have time to rearrange to the less crowded and, therefore, the more stable σ-allyl complex **B** and reductive elimination from the latter would give the α-product.



Scheme 1.15. Proposed mechanism of copper-catalyzed allylic substitution reaction.

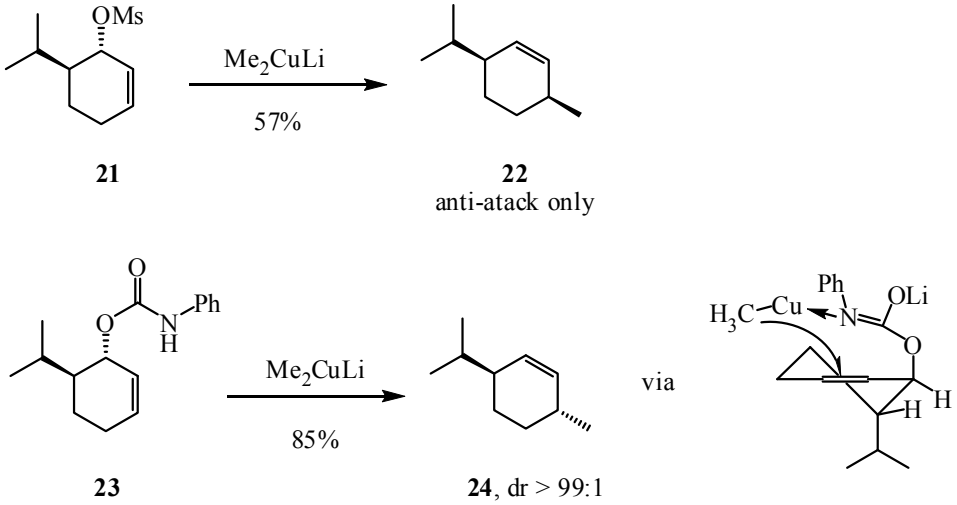
It is worth noting that γ-regioselective substitution reactions between γ-substituted primary allylic substrates and organocopper reagents (γ-S_{AL}) lead to the creation of new chiral centers in previously achiral substrates. Serious efforts were made to take advantage of this for the development of enantioselective allylic substitution reactions exploiting chiral leaving groups,[39] chiral auxiliaries that are removed after the reaction[40] and catalytic reactions with chiral ligands.[41]

To explain the anti-stereochemistry of the γ-allylic substitution reactions (γ-S_{AL}),[34] a simple stereoelectronic model based on frontier molecular orbital considerations has been proposed[42] (Scheme 1.16). Organocopper reagents, unlike C-nucleophiles, possess filled d^{10}-orbitals, which can interact both with the π*-(C=C) orbital at the γ-carbon and to a minor extent with the σ*- (C-X) orbital, as shown in Scheme 1.16. To achieve optimal orbital overlap, the σ*-orbital of the C-X bond should be aligned to the alkene π-system.



Scheme 1.16. Stereochemistry of copper-mediated allylic substitution.

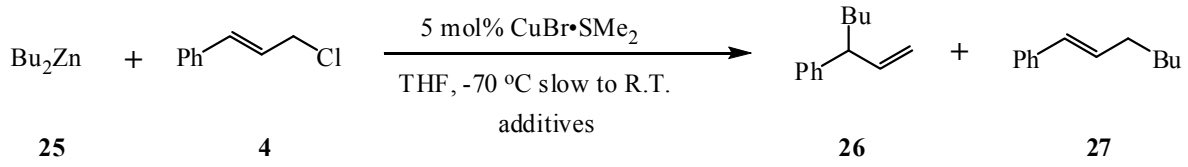
However, this intrinsic stereoelectronic control over allylic substitution can be overridden when a reagent-coordinating leaving group is in use. Suitable leaving groups were found among carbamates[43,44] (Scheme 1.17) and benzothiazoles.[45]



Scheme 1.17. Different stereochemical results with mesylate **21** and carbamate **23** leaving group during allylic substitution with cuprates.

When the non-coordinating mesylate system **21** was treated with lithium dimethylcuprate, formation of the anti-γ-S_{AL} product **22** was observed. Notably, the exclusive formation of the γ-S_{AL} product is the result of severe steric hindrance at the α-position, originating from the adjacent isopropyl group.[46]

In 1987, Nakamura discovered that copper-catalyzed reactions between dibutylzinc (*n*-Bu_2Zn) **25** with cinnamyl chloride **4**, in the presence of certain polar additives such as 2 equiv of HMPA, leads to a quantitative yield of very predominantly γ-S_{AL}-product **26**[47] as seen in Table 1.1 and depicted in Scheme 1.18. BF_3•Et_2O, which dramatically enhances γ-regioselectivity for Yamamoto reagents (RCu),[25] appeared ineffective this time.[47]



Scheme 1.18. γ-Regioselective copper mediated alkylation of cinnamyl chloride with butylzinc chloride and dibutylzinc.

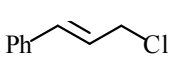
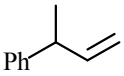
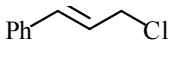
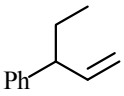
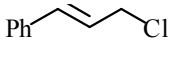
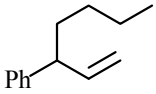
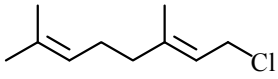
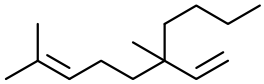
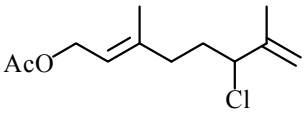
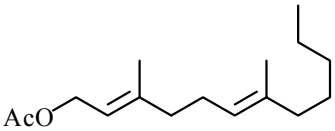
Table 1.1. Copper Catalyzed Reaction of Bu_2Zn with Cinnamyl Chloride[47]

Entry	*Cu(I) %*	*HMPA equiv*	*DMF vol%*	*BF_3•Et_2O equiv*	*% yield*	*γ:α product*
1					trace	
2	5				18	67:33
3	5	2			100	97:3
4	5		50		100	96:4
5	5			2	14	71:29
6	100	2			78	86:14

It was also noted that the γ/α-substitution ratio is particularly high when the γ-carbon atom bears no substituents or when the α-carbon atom possesses substituents.[47] The nature of the bulk solvent was also claimed to be important for the regioselectivity as well as for the reaction rate.[48] The reaction in pure hexane was found to be extremely slow, while the reaction in TMEDA/hexane is less selective and much slower than the reaction in TMEDA/THF. Thus, THF has proved to be the bulk solvent of choice for fast and γ-regioselective copper catalyzed reactions between allylic chlorides and alkylzincs.

Some successful γ-regioselective substitution reactions of only methyl and primary alkylzincs with some allylic systems were reported by Nakamura in 1988.[49]

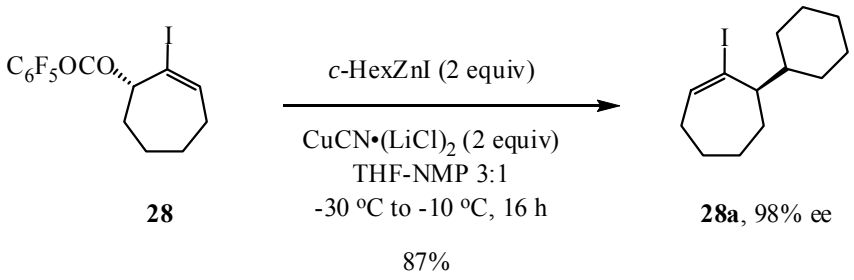
Table 1.2. Copper Catalyzed γ-S_{AL} Allylation of Organozinc Reagents in THF[a]

Entry	*Alkylzinc*	*Substrate*	*γ-substitution product*	*γ:α product*	*Yield %*
1	MeZnCl			98 : 2	67
2	Et_2Zn			98 : 2	85
3	BuZnCl			96 : 4	84
4	BuZnCl			91 : 9	62
5	BuZnCl			100 : 0	65

[a] The allylic chloride was allowed to react in THF with the zinc reagent (1 – 1.5 equiv) at 0 – 20 °C for 5 – 15 h. In entries 1, 2 and 4, HMPA (1 equiv) was used as an additive. $CuBr•SMe_2$ (5 mol%) was used as a catalyst. The isomeric ratio was determined by capillary GLC analysis, and the regio- and stereochemical assignment was made by IR and 300 MHz ^{1}H NMR analysis.

It is noticeable that the major problem with known S_N2' attacks of organozincs on allylic chlorides is the lack of generality. Primary organozincs have been examined while the only one reported attempt using a more substituted organozinc *t*-$Bu_2Zn•2LiCl$ in the reaction with 4-phenyl-1-chloro-2-pentene, in the presence of HMPA rather than a cuprous salt, was found to have virtually no regioselectivity.[48] Only after most of the work in this thesis was completed, the use of a secondary alkylzinc reagent in γ-allylic substitution reactions in the presence of a large

amount of toxic and hygroscopic CuCN•2LiCl was reported by Knochel and co-workers.[50] Moreover, two rather than one equivalents of the organozinc reagent were used (Fig 1.19).



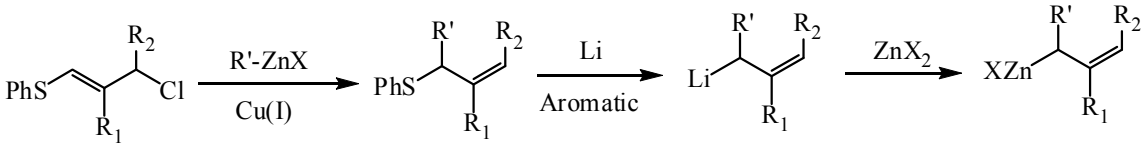
28 **28a**, 98% ee

Scheme 1.19. Recently reported γ-allylic substitution reaction using a secondary alkylzinc reagent in the presence of a large amount of CuCN•2LiCl.

1.2 RESULTS AND DISCUSSION

1.2.1 General considerations

1-Phenylthio-3-chloropropenes **29** contain two functional groups that make them versatile synthons in organic synthesis. The allyl chloride moiety can be exploited in γ-S_{AL} copper mediated reactions to construct γ-substituted allyl phenyl sulfides **30**. Compounds **30** are splendid precursors of various allyllithiums which, in turn, can be used in a number of ways including transmetallation to allylzinc compounds. Alternatively, the generated allyl phenyl sulfides can be easily oxidized to sulfones to be converted into allylzincs in Pd-catalyzed reactions in order to maintain high tolerance for most functional groups which might be introduced into **30** in a prior γ-S_{AL} reaction of **29** with an organozinc reagent (Fig 1.20).



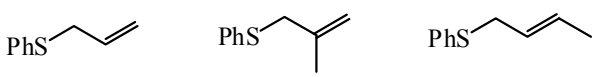
29 **30** **31** **32**

Scheme 1.20. Reductive lithiation of ally phenyl sulfides derived from γ-substitution in 1-phenylthio-3-chloropropenes.

Because neither optimum reaction conditions of copper catalyzed organozinc γ-S_{AL} substitutions nor the scope and limitations have been well defined and because 1-phenylthio-3-chloropropenes have never been used as organic substrates for such reactions, the possibility of using the latter was examined and the best conditions for different types of organozincs were established.

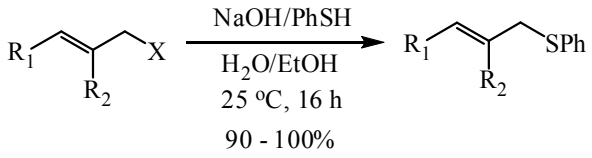
1.2.2 Preparation of Allyl Phenyl Sulfides and 1-Phenylthio-3-chloropropenes

Three allyl phenyl sulfides **33 – 35** (Scheme 1.21) were prepared in high yields by S_N2 reactions between NaSPh, generated from thiophenol and sodium hydroxide in water solution, and the corresponding allyl halides (Scheme 1.22).



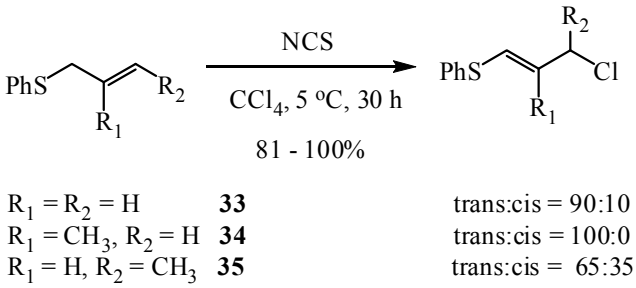
33 **34** **35**

Scheme 1.21. Allyl phenyl sulfides produced in S_N2 reactions with allyl halides.



Scheme 1.22. Preparation allyl phenyl sulfides **33-35** by S_N2 reactions with NaSPh.

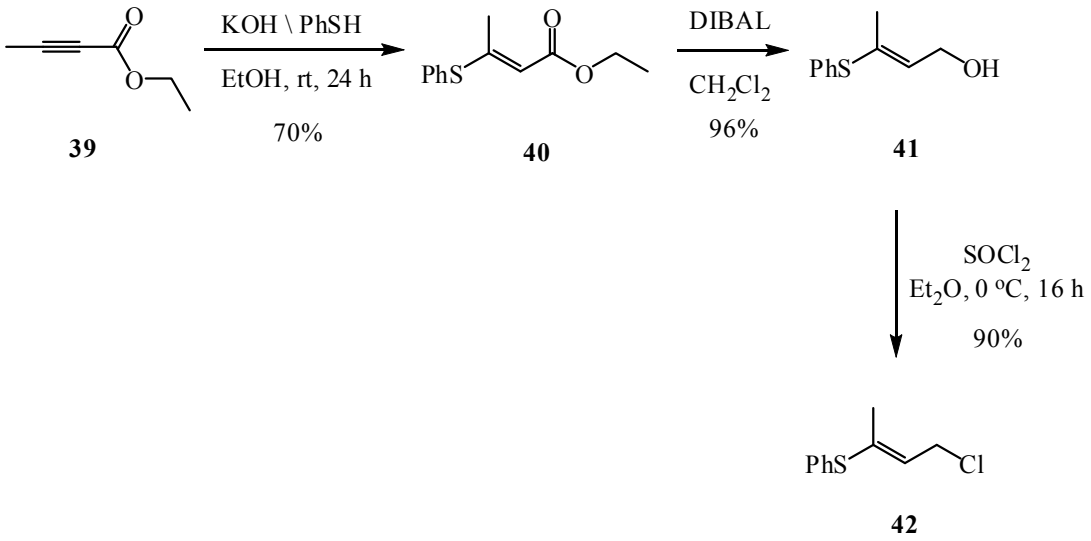
1-Phenylthio-3-chloropropenes **36**, **37** and **38** were synthesized in nearly quantitative yields utilizing the method developed in this laboratory,[51] which involves chlorination of the corresponding allyl phenyl sulfides with *N*-chlorosuccinimide (NCS) at 5 °C for 30 h (Fig 1.23).



$R_1 = R_2 = H$	**33**	trans:cis = 90:10	**36**
$R_1 = CH_3$, $R_2 = H$	**34**	trans:cis = 100:0	**37**
$R_1 = H$, $R_2 = CH_3$	**35**	trans:cis = 65:35	**38**

Scheme 1.23. Chlorination of allyl phenyl sulfides with NCS in CCl_4.

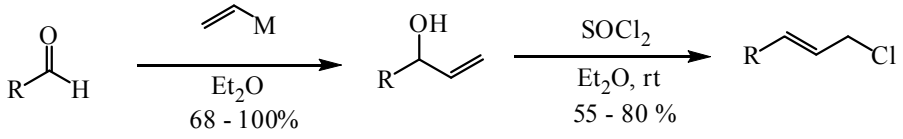
The γ-methyl substituted 3-phenylthio-1-chloro-2-butene **42** was prepared in the reaction sequence depicted in Scheme 1.24.



Scheme 1.24. Preparation of 3-phenylthio-1-chloro-2-butene **42**.

1.2.3 Preparation of Other Substituted Allyl Chlorides and Phosphoric Esters

Terminal allyl chlorides **49 – 51** were prepared using S_Ni' reactions between the corresponding allyl alcohols **46** – **48** and thionyl chloride as a key step (Scheme 1.25).[52]



43 R = *o*-Tolyl
44 R = $CH_3(CH_2)_6CH_2$
45 R = $CH_3(CH_2)_2CH(CH_3)$

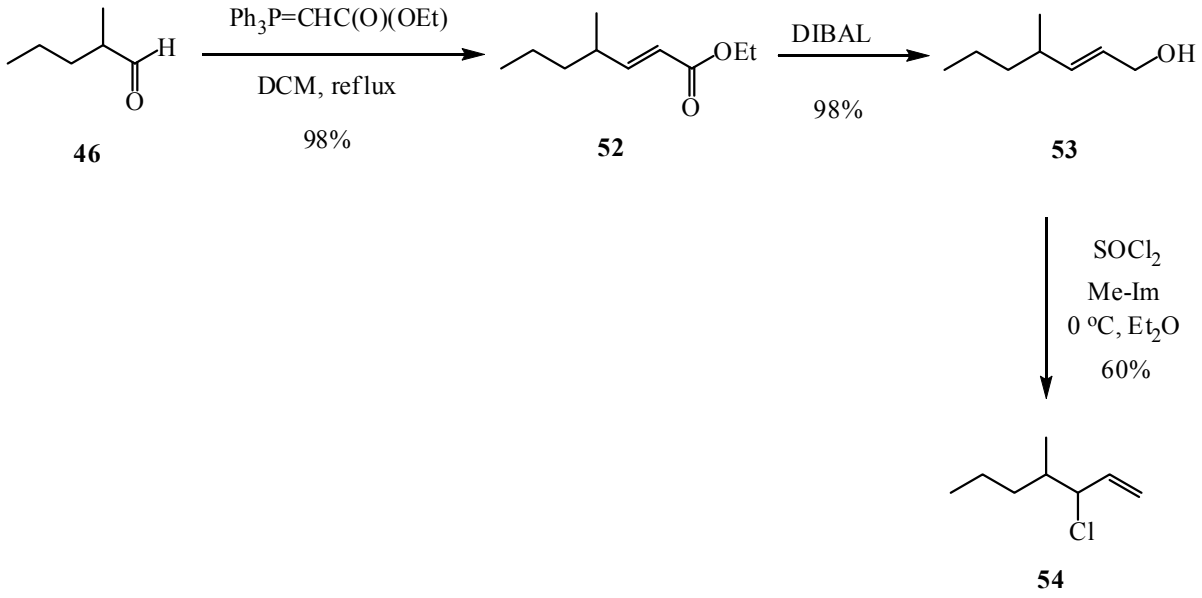
46 R = *o*-Tolyl
47 R = $CH_3(CH_2)_6CH_2$
48 R = $CH_3(CH_2)_2CH(CH_3)$

49 R = *o*-Tolyl
50 R = $CH_3(CH_2)_6CH_2$
51 R = $CH_3(CH_2)_2CH(CH_3)$

M = Li, MgBr and MgCl

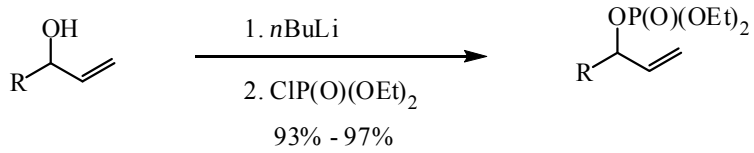
Scheme 1.25. Preparation of terminal allyl chlorides.

Using the same S_Ni' key step, allyl chloride **54** was prepared as depicted in Scheme 1.26.



Scheme 1.26. Preparation of allyl chloride **54**.

Allyl phosphoric esters **56** and **57** were prepared in high yields from the corresponding alcohols **48** and **55** as shown in Scheme 1.27.



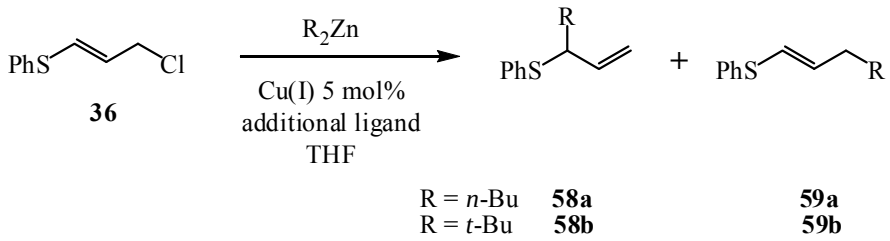
48 R = $CH_3(CH_2)_2CH(CH_3)$
55 R = C_5H_{11}

56 R = $CH_3(CH_2)_2CH(CH_3)$
57 R = C_5H_{11}

Scheme 1.27. Preparation of allyl phosphoric esters.

1.2.4 Dialkylzincs (R_2Zn) in Model Copper Catalyzed γ-Substitution Reactions with 1-Phenylthio-3-chloropropene

1-Phenylthio-3-chloropropene **36** is the simplest prototypical probe used for the study of copper catalyzed γ-substitution reactions of dialkylzincs, including primary, secondary and tertiary dialkylzinc reagents. Di-*n*-butyl-, di-*sec*-butyl- and di-*tert*-butylzincs were prepared in transmetallation reactions with the corresponding alkyllithium reagents at -78 °C during 40 min. A catalytic amount of CuBr•SMe_2 (5 mol %) and/or 1 equiv of additional ligand TMEDA was added (Scheme 1.28). It was found that the presence of a catalytic amount of Cu(I) is the key to a successful reaction, regardless of the actual form of the catalyst used, while an additional chelating ligand, TMEDA, obviously, plays no role in the reaction (Table 1.3).



Scheme 1.28. γ-Allylic substitution reactions between **36** and dialkylzincs.

Table 1.3. Reactivity and regioselectivity of R_2Zn reagents in various reaction conditions [a]

Entry	*R_2Zn[b]*	*Cu(I) 5 mol%*	*Additive*	*% Yield (58+59)[c]*	*$\gamma:\alpha$ product (58:59)[d]*
1	*n*-Bu_2Zn	-	-	0	
2	*n*-Bu_2Zn	-	TMEDA 1 equiv	0	
3	*t*-Bu_2Zn	-	TMEDA 1 equiv	0	
4	*n*-Bu_2Zn	CuBr•SMe_2	TMEDA 1 equiv	97	>95:5
5	*t*-Bu_2Zn	CuBr•SMe_2	TMEDA 1 equiv	94	95:5
6	*t*-Bu_2Zn	CuBr•SMe_2	NA	98	>95:5
7	*t*-Bu_2Zn	CuCN•2LiCl	NA	98	>95:5
8	*n*-Bu_2Zn	CuCN•2LiCl	NA	96	>95:5
9	*n*-Bu_2Zn	CuBr•SMe_2	NA	98	>95:5

[a] The ratio of 1-phenylthio-3-chloropropene : R_2Zn (~0.01 M THF solution) used was 1 : 1.5 in all reactions. Components were mixed at -78 °C and then reaction mixtures were allowed to slowly warm to ambient temperature. [b] All dialkylzinc reagents R_2Zn were prepared by the reaction between 2 equiv of the corresponding RLi and 1 equiv of $ZnCl_2$ or $ZnBr_2$ in THF at -78 °C. [c] Yields are based on the use of only one of the two R-groups. [d] The product ratios were determined by ^1H NMR.

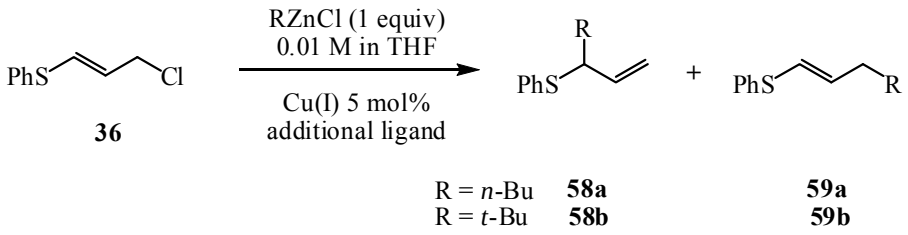
Each copper-catalyzed reaction is extremely γ-regioselective and proceeds in nearly quantitative yield. It is remarkable, and it has been clearly shown for the first time, that primary, secondary and tertiary dialkylzincs can be used equally with the same high yields and unprecedented γ-regioselectivity. Thus, tertiary alkyl substituted allyl sulfides of type **58b** now become quite readily available and the major limitation of the classical connective synthetic pathway, is overcome. The major drawback, however, is still that one of the two alkyl groups of the dialkylzinc reagent is wasted in the reaction. It might be tolerable for dialkylzincs prepared from commercially available alkyllithiums and used then in model experiments, but not when the alkyl group is more difficult to generate.

Thus, it is important to establish conditions in which a stoichiometric amount of monoalkylzinc reagents can be successfully used instead of dialkylzincs.

1.2.5 Monoalkylzincs (RZnX) in Model Copper Catalyzed γ-Substitution Reactions with 1-Phenylthio-3-chloropropene

Monoalkylzincs appear to be far less reactive compounds than dialkylzincs. Preliminary experiments were carried out under the same conditions which were found appropriate for dialkylzincs including the presence of the additional ligands TMEDA or (-)-sparteine. Thus, 0.01 M THF solutions of organozincs were prepared by transmetallation with 1 equiv of the corresponding alkyllithiums and then the Cu(I) catalyst and between 1.0 and 2.2 equiv of an additional ligand were added (Scheme 1.29). The results are given in Table 1.4.

When performed in low concentration solutions of organometallics (0.01 M THF solution), reactions of monoalkylzinc reagents with compound **36** are still extremely γ-regioselective and occur only in the presence of a chelating additive (Scheme 1.29, Table 1.4). However, either a full equiv of (-)-sparteine ligand or at least 2.2 equiv of TMEDA is required to obtained γ-substitution products **58a** and **58b** in high yields (Table 1.4).



Scheme 1.29. γ-Allylic substitution reactions between 1-phenylthio-3-chloropropene **36** and monoalkylzincs in low concentration THF solutions (~0.01 M).

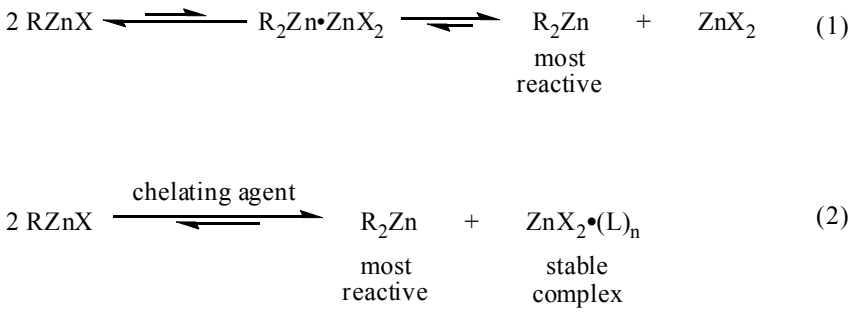
Table 1.4. Reactivity and regioselectivity of RZnCl reagents in 0.01 M THF solution [a]

N	*RZnCl* [b]	*Cu(I) 5mol%*	*Additive*	*% Yield (58+59)*	*γ:α product (58:59)* [c]
1	*n*-BuZnCl	CuBr•SMe_2	NA	traces	-
2	*n*-BuZnCl	-	TMEDA 1 equiv	0	-
3	*n*-BuZnCl	CuBr•SMe_2	TMEDA 1 equiv	52%	>95:5
4	*n*-BuZnCl	CuBr•SMe_2	TMEDA 1.3 equiv	64%	>95:5
5	*n*-BuZnCl	CuBr•SMe_2	TMEDA 2.2 equiv	98%	>95:5
6	*t*-BuZnCl	CuBr•SMe_2	TMEDA 2.2 equiv	ca. 100%	>95:5
7	*n*-BuZnCl	CuBr•SMe_2	(-)-sparteine 1 equiv	92%	>95:5
8	*t*-BuZnCl	CuBr•SMe_2	(-)-sparteine 1 equiv	95%	>95:5

[a] The ratio of 3-chloro-allylphenyl sulfide : RZnCl (~0.01 M THF solution) used was 1.0 : 1.2 in all reactions. Components were mixed at -78 °C and then reaction mixtures were allowed to slowly warm to ambient temperature for overnight. [b] All alkylzinc halides RZnCl were prepared by the reaction between 1 equiv of RLi and 1 equiv of $ZnCl_2$ solution in THF at -78 °C. [c] The product ratios were determined by ^{1}H NMR.

A reasonable explanation of the results given in Table 1.4 is that the reactive species is a zinc dialkylcuprate that is produced far faster when the organometallic is a dialkylzinc rather than a monoalkylzinc halide. Since TMEDA is known to strongly complex zinc halides,[17] this chelating agent is expected to shift the Schlenk equilibrium (Fig 1.30, Eq. 1)[18,19] to the right, thus

increasing the concentration of the dialkylzinc, which is made available for cuprate formation (Scheme 1.30, Eq. 2).

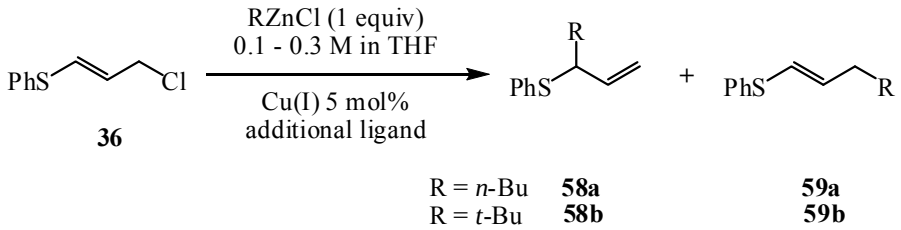


Scheme 1.30. Schlenk equilibrium shifted to the right by a chelating agent.

Consistent with this hypothesis is the discovery that only one equiv of the ligand (-)-sparteine, which forms a highly stable 1:1 adduct with $ZnMe_2$[53] and would be expected to form an even stronger complex with $ZnCl_2$,[17] provides yields close to quantitative.

However, it was discovered that high yields and selectivity could also be obtained even in the absence of any complexing agent when high concentrations (0.1 – 0.3 M) of monoalkylzinc reagents were applied (Scheme 1.31, Table 1.5). This highly significant and satisfying result can not be explained in an obvious way by the traditional form of the Schlenk equilibrium but it can be readily rationalized by a form of the Schlenk equilibrium that has been used more recently[19,54] and is shown in Scheme 1.30 (Eq. 1). The increase in concentration of **RZnX** results in shifting of the Schlenk equilibrium to the right providing a greater concentration of the complex **ZnR_2•ZnX_2** (Fig 1.30, Eq. 1)[54] which may also be more reactive than the monoalkylzinc halide. It is gratifying that increasing the concentration in THF 10-fold (to 0.1 – 0.3 M) allows excellent

yields and γ-selectivity in 16 – 24 h without the use of a chelating agent (Table 1.5), which makes reaction conditions suggested by Nakamura[47,48,49] obsolete.



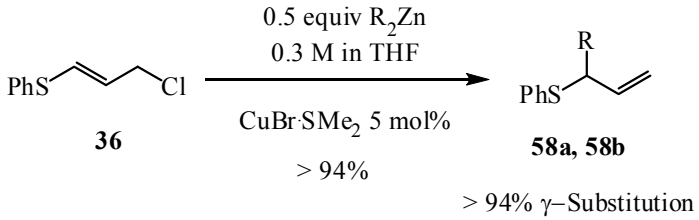
Scheme 1.31. γ-Allylic substitution reactions between 1-phenylthio-3-chloropropene **36** and monoalkylzincs in concentrated THF solutions (0.1 – 0.3 M).

Table 1.5. Reactivity and regioselectivity of RZnCl reagents in concentrated THF solutions

N	*RZnCl*	*Additive*	*Cu(I)*	*Concentration*	*% Yield*	*γ:α product* [a]
1	*n*-BuZnCl	TMEDA 1 equiv	$CuBr•SMe_2$	0.10 M	82%	92:8
2	*n*-BuZnCl	TMEDA 2 equiv	$CuBr•SMe_2$	0.10 M	94%	92:8
3	*n*-BuZnCl	-	$CuBr•SMe_2$	0.30 M	92%	94:6
4	*t*-BuZnCl	TMEDA 1 equiv	$CuBr•SMe_2$	0.15 M	90%	>95:5
5	*t*-BuZnCl	(-)-sparteine 1 equiv	$CuBr•SMe_2$	0.15 M	98%	>95:5
6	*t*-BuZnCl	-	$CuBr•SMe_2$	0.30 M	97%	>95:5

[a] The product ratios were determined by ^1H NMR

As a consequence, in concentrated THF solutions (0.1 – 0.3 M) only 0.5 equiv of dialkylzincs R_2Zn in the presence of a catalytic amount of $CuBr{\bullet}SMe_2$ (5 mol %) is enough to carry out γ-regioselective reactions with almost quantitative yields (Scheme 1.32). In other words, under these conditions both alkyl groups of the dialkylzinc are used.



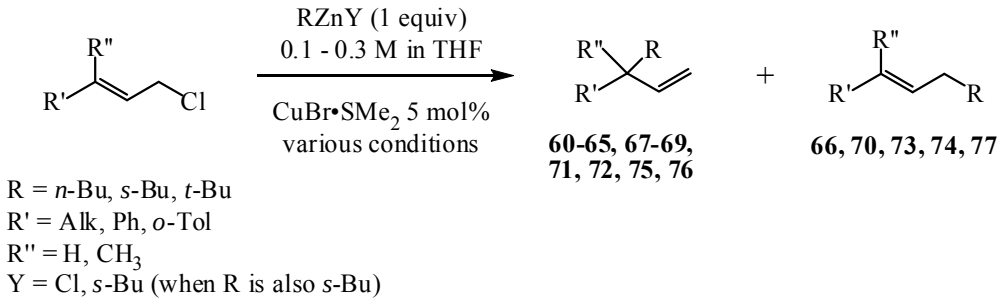
Scheme 1.32. In concentrated THF solutions (0.1 – 0.3 M), only 0.5 equiv of dialkylzincs R_2Zn is enough to carry out γ-regioselective reactions in nearly quantitative yields.

Additional ligands might also be found useful to accelerate the reactions if low concentrations of monoalkylzincs are to be used.

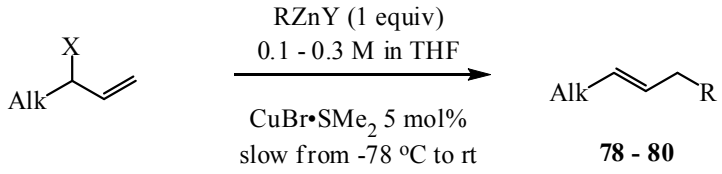
1.2.6 Monoalkylzincs (RZnX) in Model Copper Catalyzed γ-Substitution Reactions with Various Allyl Chlorides. Scope and Limitations.

In order to further investigate copper catalyzed γ-substitution reactions of all types of monoalkylzinc reagents, various allyl chloride substrates have been examined under different conditions. Under the "standard" conditions (A), when the actual reaction starts at -78 °C and the mixture is allowed to warm slowly to ambient temperature in 4 – 8 h, primary, secondary and tertiary alkylzinc chlorides, prepared by transmetallation of the alkyllithiums, react in excellent

yield and γ-regioselectively with relatively unhindered straight chain allyl chlorides (Scheme 1.33 and Table 1.6, entries 1-3). While the greater γ steric hindrance provided by the phenyl group of *E*-cinnamyl chloride allows equally good results with primary and secondary butylzinc chloride under the standard conditions (A) (Table 1.6, entries 4 and 6), γ-regioselectivity is seriously eroded when the alkyl group is tertiary (entry 7). The problem was compounded when allyl chlorides possessed larger substituents at the γ-carbon atoms (Scheme 1.33 and Table 1, entries 12, 17 and 23) and when certain reactions were carried out at low temperature (-70 °C) (Scheme 1.33 and Table 1, conditions (B) entries 8 and 18). Although, generally speaking, dialkylzinc reagents are far more reactive than monoalkylzincs, it is important to mention that the reactivity of *t*-BuZnCl is much greater than that of *n*-Bu_2Zn and close to that of *sec*-Bu_2Zn. Both, *t*-BuZnCl and *sec*-Bu_2Zn, are able to react with the allyl chlorides under investigation in the presence of a CuBr•SMe_2 catalyst at as low temperature as -70 °C (Scheme 1.33 and Table 1.6, entries 8 and 18). On the other hand, *n*-Bu_2Zn, *sec*-BuZnCl and *n*-BuZnCl are not reactive enough to give noticeable results at temperatures below -20 °C.



R = *n*-Bu, *s*-Bu, *t*-Bu
R' = Alk, Ph, *o*-Tol
R'' = H, CH_3
Y = Cl, *s*-Bu (when R is also *s*-Bu)

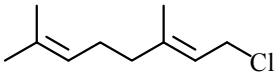
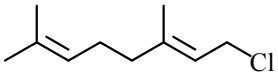
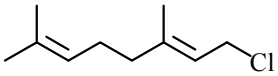
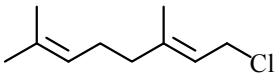
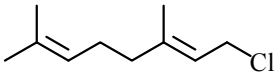
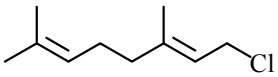
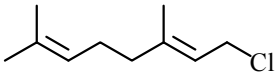
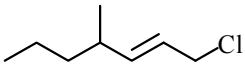
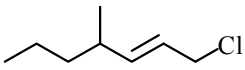
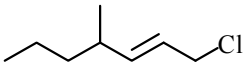
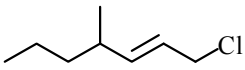


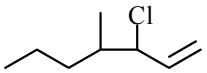
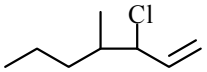
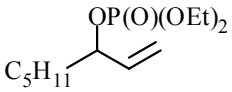
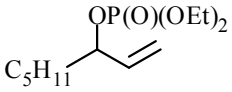
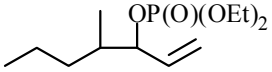
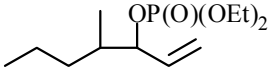
R = *n*-Bu, *s*-Bu, *t*-Bu
Alk = $CH_3(CH_2)_2CH(CH_3)$, C_5H_{11}
X = Cl, $OP(O)(OEt)_2$

Scheme 1.33. Alkylation of various allyl halides with primary, secondary and tertiary alkylzinc reagents catalyzed by $CuBr•SMe_2$ in concentrated THF solutions (0.1 – 0.3 M).

Table 1.6. γ- and α-Alkylation of Allyl Chlorides by Monoalkylzincs in the Presence of Catalytic $CuBr•SMe_2$

N	*R'ZnCl*	*T ℃ conditions*[a]	*Substrate*[b]	*Product ratio γ:α*[c]	*Major Product #*	*Isolated yield %*
1	*n*-BuZnCl	(A)	$C_8H_{17}CH=CHCH_2Cl$	> 95 : 5	**60**	92
2	*s*-BuZnCl	(A)	$C_8H_{17}CH=CHCH_2Cl$	> 95 : 5	**61**	90
3	*t*-BuZnCl	(A)	$C_8H_{17}CH=CHCH_2Cl$	> 95 : 5	**62**	98
4	*n*-BuZnCl	(A)	$PhCH=CHCH_2Cl$	> 95 : 5	**63**	92
5	*n*-BuZnCl	(B)	$PhCH=CHCH_2Cl$	-		0
6	*s*-BuZnCl	(A)	$PhCH=CHCH_2Cl$	> 95 : 5	**64**	91
7	*t*-BuZnCl	(A)	$PhCH=CHCH_2Cl$	33 : 67	**65, 66**	100
8	*t*-BuZnCl	(B)	$PhCH=CHCH_2Cl$	9 : 91	**66**	67
9	*t*-BuZnCl	(C)	$PhCH=CHCH_2Cl$	95 : 5	**65**	91
10	*n*-BuZnCl	(A)	*o*-Tol-$CH=CHCH_2Cl$	93 : 7	**67**	96
11	*s*-BuZnCl	(A)	*o*-Tol-$CH=CHCH_2Cl$	> 95 : 5	**68**	93
12	*t*-BuZnCl	(A)	*o*-Tol-$CH=CHCH_2Cl$	20 : 80	**69, 70**	95

13	*t*-BuZnCl	(C)	*o*-Tol-CH=CHCH$_2$Cl	> 95 : 5	**69**	98
14	*t*-BuZnCl	(B)	*o*-Tol-CH=CHCH$_2$Cl	6 : 94	**70**	76
15	*n*-BuZnCl	(A)		> 95 : 5	**71**	100
16	*s*-BuZnCl	(A)		>95 : 5	**72**	94
17	*s*-BuZnCl	(B)		-		0
18	*s*-Bu$_2$Zn	(A)		< 5 : 95	**73**	100
19	*s*-Bu$_2$Zn	(B)		< 5 : 95	**73**	100
20	*s*-Bu$_2$Zn	(C)		67 : 33	**72, 73**	100
21	*t*-BuZnCl	(C)		< 5 : 95	**74**	86
22	*n*-BuZnCl	(A)		87 : 13	**75**	72
23	*n*-BuZnCl	(C)		87 : 13	**75**	96
24	*t*-BuZnCl	(A)		20 : 80	**76, 77**	83
25	*t*-BuZnCl	(C)		88 : 12	**76**	94

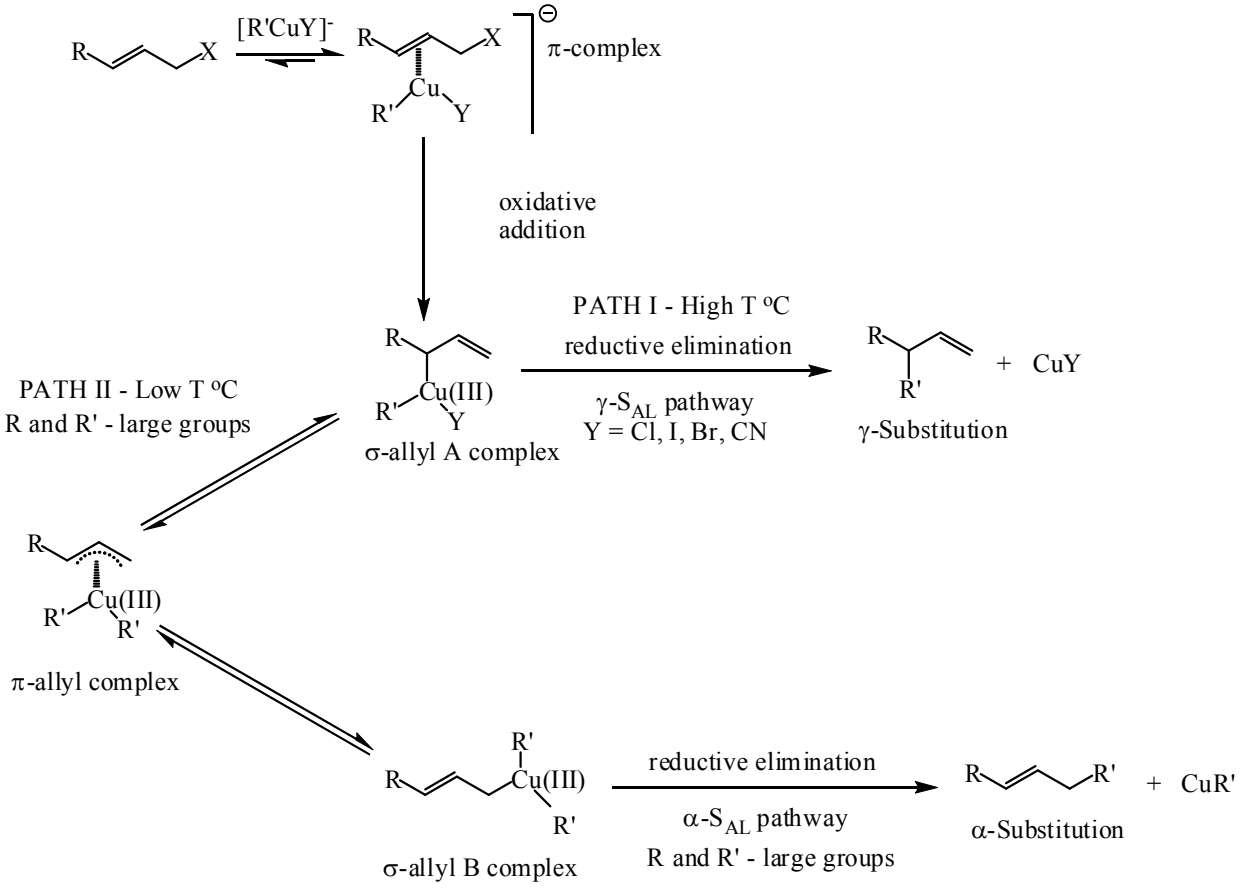
26	*n*-BuZnCl	(A)		> 95 : 5	**78**	97
27	*t*-BuZnCl	(A)		> 95 : 5	**76**	98
28	*n*-BuZnCl	(A)		> 95 : 5	**79**	91
29	*t*-BuZnCl	(A)		> 95 : 5	**80**	97
30	*n*-BuZnCl	(A)		> 95 : 5	**78**	100
31	*t*-BuZnCl	(A)		> 95 : 5	**76**	100

[a] The CuBr•Me_2S was used in catalytic amounts, 5 mol %. Conditions (A): a reaction starts at -78 °C and a mixture is allowed to warm slowly to ambient temperature, 4 – 8 h; Conditions (B): a reaction proceeds at a constant -70 °C for 24 h; Conditions (C): a reaction proceeds at a constant 0 °C for 36 h. [b] All allyl halides have the E-configuration. [c] The product ratios were determined by ^{1}H NMR.

To our knowledge there is only one other report of such a temperature effect on the regioselectivity of nucleophilic displacement in an allylic system. Among a number of other effects, Backvall *et al*[36] reported that lower temperatures favor α-attack and higher temperatures γ-attack in the reactions of Grignard reagents with allyl acetates under catalysis of Li_2CuCl_4 and CuCN.

A plausible rationalization of the temperature effect is given in Scheme 1.34 and is based on the different sensitivities to temperature of two potential conversions of the copper (III)

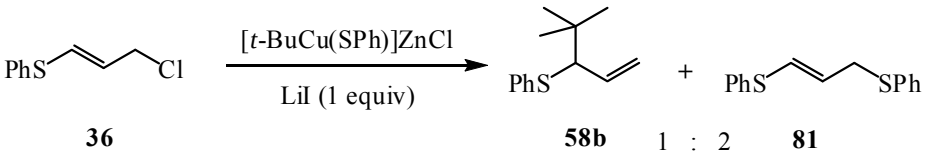
adduct **A** to the γ-substitution product by reductive elimination (path I) and conversion to the σ-complex **B** via the π-complex **C** (path II). The different temperature sensitivities of these paths arise because they probably have different entropies of activation due to the fact that path I causes the release of more particles than path II, including precipitation of CuY. This becomes important when the γ-position in **A** is congested due to the large size of R and R'. In that situation, the usual tendency of path I being faster than the path II (especially when Y is an electron withdrawing group such as Br, CN or SPh) can be reversed because path I brings the larger groups closer while path II leads to a greater separation. Under these conditions, raising the temperature in order to favor path I becomes extremely important.



Scheme 1.34. Proposed rationalization of the temperature effect in α:γ-selectivity.

Although, a temperature of 0 °C seems to be the most general approach for all types of monoalkylzincs and allyl chloride substrates, due to the thermal instability of the copper bromide catalyst at high temperatures in organozinc reagent solutions, it is recommend to use such conditions only when general conditions (A) fail.

An attractive method to overcome the 0 °C restriction for CuBr•SMe_2 catalyst, is to replace the catalyst cuprous bromide with the chemically and thermally stable non-toxic cuprous thiophenoxide (CuSPh) catalyst, although the insolubility of CuSPh in THF requires a longer time (48 hours and longer). In this case, the reaction rate can be dramatically increased by use of a stoichiometric amount of CuSPh. This experimental observation, used below in the Experimental Parts of Chapters 3 and 4, should become widely used in syntheses. It is worthwhile to note that the presence of a significant amount of iodide ion (I^-) in a reaction mixture with CuSPh causes significant SPh-transfer at the α-position due to displacement of the soft SPh-group at copper by iodide forming the strong S_N2 nucleophile SPh^- (Scheme 1.35).



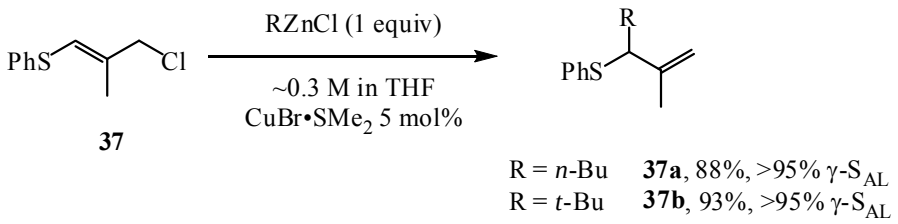
Scheme 1.35. SPh-group is transferable in the presence of significant amount of I^-.

It is highly recommended that only CuSPh be tried instead of CuCN•2LiCl, which is also stable at room temperature, in cases in which a mixed Zn heterocuprate reagent is desired, because of the significant safety and environmental problems associated with the use of

cyanides, especially in stoichiometric amounts[55] and also because of expensive dry LiCl being used in 2 molar equivalents.

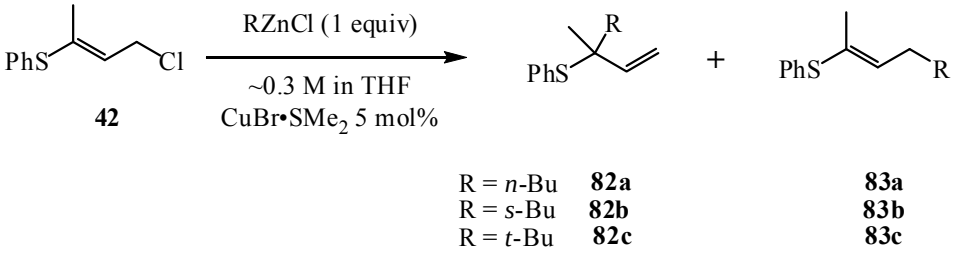
It is noteworthy that the reaction conditions proposed for allyl chlorides are equally applicable for diethyl phosphate allylic substrates, which were also successfully used in S_N2' reactions with monoalkylzinc reagents catalyzed by CuBr•SMe_2 (Table 1.6, entries 28-31).

While alkyl substituents at C-2 and C-3, as in 2-methyl-1-phenylthio-3-chloropropene **37**, do not affect reactivity and regioselectivity (Scheme 1.36), an alkyl substituent, at the C-1 position, even as small as methyl, is able to shift regioselectivity completely from γ- to α- in certain cases (Scheme 1.37, Table 1.7).



Scheme 1.36. Methyl substituent in **37** at a non-γ position does not affect reactivity and regioselectivity.

The use of 3-thiophenyl-1-chloro-2-butene **42** in reactions with various types of monoalkylzincs in general reaction conditions (A) resulted in regioselectivity (Scheme 1.37, Table 1.7) that could be reliably predicted based on data given in Table 1.6 for geranyl chloride.



Scheme 1.37. Reaction of 2-thiophenyl-4-chloro-2-butene **42** with various types of monoalkylzincs.

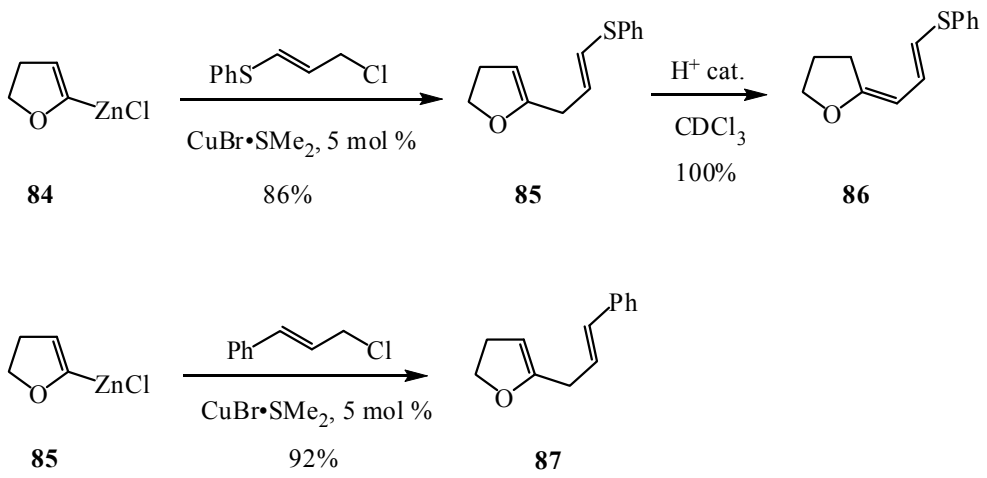
Table 1.7. Alkylation of **42** by Monoalkylzincs in the Presence of Catalytic CuBr•SMe_2

N	***RZnCl***	***T ℃ conditions***[a]	***Product ratio 82:83***[b]	***Isolated yield %***
1	*n*-BuZnCl	(A)	> 95 : 5	88
2	*s*-BuZnCl	(A)	> 95 : 5	82
3	*t*-BuZnCl	(A)	< 5 : 95	91
4	*t*-BuZnCl	(C)	< 5 :9 5	85

[a] The CuBr•Me_2S was used in catalytic amounts, 5 mol %. Conditions (A): reaction starts at -78 °C and a mixture is allowed to warm slowly to ambient temperature, 4 – 8 h; Conditions (C): reaction proceeds at constant 0 °C for 36 h.

[b]NMR ratios.

Our preliminary results, observed for only one type of vinylzinc **84** (Scheme 1.38), have demonstrated the exclusive formation of only α-substitution products **85** and **87**, which is diametrically opposite to the results observed for alkylzinc reagents.



Scheme 1.38. Copper (I) catalyzed reaction of vinylzinc **84** and 1-phenylthio-3-chloropropene and cinnamyl chloride results in α-substitution products **85** and **87**.

1.2.7 Conclusions

It has been found that dialkylzincs, when used in equimolar amounts with the allyl halide substrates, require no additional ligand of any kind to give nearly quantitative yields in copper(I) catalyzed γ-allylic substitution. The disadvantage of using equimolar dialkylzincs is that one of the two alkyl groups is wasted in the reaction and so the use of monoalkylzincs was explored.

Monoalkylzinc reagents were found to be reactive enough to give nearly quantitative yields and extremely high γ-regioselectivity either in highly concentrated ethereal solutions or in solutions of low concentration in the presence of certain additional ligands, such as TMEDA or (-)-sparteine. Both concentration and additional ligand effects are explained by the use of a mechanistic model that includes shifting the Schlenk equilibrium in favor of the dialkylzinc reagent either by the concentration effect or by removing $ZnCl_2$ due to the formation of stable complexes with the additional ligand.

Thus, Nakamura's conditions, which advanced the field greatly when they were originally revealed, are now obsolete, and new general conditions, which require only 1 equivalent of a monoalkylzinc reagent in highly concentrated ethereal solution (≥ 0.3 M) and 5 molar % of $CuBr•SMe_2$, are proposed for all types of monoalkylzincs including primary, secondary and tertiary alkyls.

Furthermore, it has been demonstrated that the extremely high γ-regio-selectivity, observed for each type of monoalkylzinc reagent, was found to be eroded when either *t*-BuZnCl or *s*-Bu_2Zn reacts with allyl chlorides possessing large substituents at the γ-carbon atoms when the reagents are mixed at -78 °C and then the reaction mixture is allowed to warm to ambient temperature slowly overnight.

A far more surprising result is that the use of increased and constant reaction temperature (0 °C) was able to resolve the problem and γ-regioselectivity was completely restored in most cases. The only failure of this protocol is when both carbon atoms of the newly produced C-C bond are tertiary and therefore extremely congested (Table 1.6, entry 21 and Scheme 1.37, R = *t*-Bu).

Finally, the scope and limitations of copper (I) catalyzed alkylzinc γ-allylic substitution reactions have been established. By use of a mechanistic model that includes some control over the Schlenk equilibrium and the use of a high temperature effect (a possible entropy effect), general, simple and reliable reaction conditions have been established for the very high yield and γ-regioselective displacement of allylic chlorides by primary, secondary and tertiary monoalkylzinc chlorides in the presence of catalytic cuprous salts as the only additives.

1.3 EXPERIMENTAL SECTION

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C at 22°C. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of the $CDCl_3$ triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). Coupling constants, J, are reported in Hz. High resolution mass spectra were recorded on a CH-5 double focusing Varian MAT or on VG 70-SE mass spectrometer.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium metal in the presence of benzophenone as indicator. Dichloromethane was freshly distilled over CaH_2. 2,3-dihydrofuran, (-)-sparteine and TMEDA were distilled over CaH_2 and stored under argon. A dry ice/acetone bath was used to obtain a temperature of -78 °C. An ice bath was used to obtain 0 °C. An ethylene glycol bath equipped with a magnetic stirrer and a cryogenic cooler Flexi-Cool FC-100 was used to obtain +5 °C.

General Experimental Procedures. All reactions were carried out under a positive pressure of dry argon gas in oven-dried (140 °C) flasks and standard precautions against moisture were taken. Flash column chromatography (low pressure) was performed either with Silicycle Silia-P Flash silica gel (40-63 μm, surface area – 500 m^2/g) or with Sigma-Aldrich basic aluminum oxide (150 mesh, 58 Å, activated). Thin-layer chromatography was performed on glass

supported 250 μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one of the following: 254 nm UV light and aqueous solution of $KMnO_4$ (1%) with NaOH (1%) and K_2CO_3 (6%). A dry ice/acetone bath was used to obtain temperatures of –78 °C. An ice bath was used to obtain 0 °C. Anhydrous magnesium sulfate was used as the drying reagent.

Vinyllithium

The following is a representative procedure for the preparation of vinyllithium. To a 1.0 M solution of vinyl bromide (42.0 mL, 42 mmol) in anhydrous ether (180 mL) at -78 °C was added *t*-butyllithium (50.0 mL, 84 mmol). The resulting mixture was stirred at -78 °C for 2 h and then slowly warmed to -20 °C. After the mixture had been stirred at -20 °C for 20 min, it was cooled to -78 °C and the vinyllithium was ready to use.

Preparation of Allyl Phenyl Sulfide (33)

A 250 mL three-neck round-bottom flask, equipped with condenser, addition funnel and glass stopper, was charged with 50 mL of water and 1.87 g (47.0 mmol) of NaOH. Thiophenol (5.0 g, 45.0 mmol) was added to the solution dropwise. The reaction mixture was stirred for 30 min to insure the complete formation of sodium thiophenoxide. Allyl bromide (4.0 mL, 46 mmol) in 7 mL of ethanol was added slowly at room temperature. The resulting reaction mixture was stirred at the same temperature for 24 h. The product was extracted with dichloromethane. The organic extract was washed with 100 mL of a 1 M aqueous solution of NaOH, and then with brine. The extract was dried over magnesium sulfate and concentrated in vacuo. The crude residue was chromatographed over basic alumina (100% hexane) to afford 6.7 g (98% yield) of allyl phenyl sulfide. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.55 – 7.28 (m, 5 H), 6.20 – 6.00 (m, 1 H), 5.32

(d, 1 H, J = 17.0 Hz), 5.25 (d, 1 H, J = 10.0 Hz), 3.71 (d, 2 H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 135.8, 133.4, 129.5, 128.5, 125.8, 117.3, 36.8. These NMR data agreed well with the literature values.[56]

2-Methyl-3-(phenylthio)propene (34).

A 500 mL three-neck round-bottom flask equipped with condenser, addition funnel and glass stopper was charged with 200 mL of water and 7.50 g (0.188 mol) of NaOH. Thiophenol (20.0 g, 0.182 mol) was added to the solution dropwise. The reaction mixture was stirred for 30 min to insure the complete formation of sodium thiophenoxide. 3-Bromo-2-methylpropene (20.0 mL, 0.185 mol) in 28 mL of ethanol was added slowly at room temperature. The resulting reaction mixture was stirred at the same temperature for 24 h. The product was extracted with dichloromethane. The organic extract was washed with 200 mL of a 1 M aqueous solution of NaOH and then with brine. The extract was dried over magnesium sulfate and concentrated in vacuo. The crude residue was chromatographed over basic alumina (100% hexane) to afford 28.6 g (96% yield) of 2-methyl-3-(phenylthio)propene (**34**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.52 – 7.32 (m, 5 H), 5.00 (s, 1 H), 4.98 (s, 1 H), 3.67 (s, 2 H), 2.01 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 140.6, 136.4, 129.8, 128.6, 126.0, 113.8, 41.7, 21.0. These NMR data agreed well with the literature values.[56] Exact mass calcd. for $C_{10}H_{12}S$ 164.0660, found 164.0657.

1-Phenylthio-2-butene (35).

A 500 mL three-neck round-bottom flask equipped with condenser, addition funnel and glass stopper was charged with 300 mL of water and 11.40 g (0.284 mol) of NaOH. Thiophenol (28.0 mL, 0.270 mol) was added to the solution dropwise. The reaction mixture was stirred for

30 min to insure the complete formation of sodium thiophenoxide. Crotyl chloride (25.0 g, 0.280 mol) in 50 mL of ethanol was added slowly at room temperature. The resulting reaction mixture was stirred at the same temperature for 24 h. The product was extracted with dichloromethane. The organic extract was washed with 200 mL of a 1 M aqueous solution of NaOH and then with brine. The extract was dried over magnesium sulfate and concentrated in vacuo. The crude residue was chromatographed over basic alumina (100% hexane) to afford 39.8 g (90% yield) of 1-phenylthio-2-butene (**35**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.33 – 7.15 (m, 5 H), 5.57 – 5.51 (m, 2 H), 3.49 (d, 2 H, J = 4.8 Hz), 1.63 (d, 3 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 136.4, 129.5, 128.9, 128.6, 126.0, 125.9, 36.3, 17.7. These NMR data agreed well with the literature values.[57] Exact mass calcd. for $C_{10}H_{12}S$ 164.0660, found 164.0659.

1-Phenylthio-3-chloropropene (36).

A 250 mL three-neck flask was charged at 5 °C with 6.8 mL (46.2 mmol) of allyl phenyl sulfide **33**, 9.14 g (68.5 mmol) of NCS and 150 mL of CCl_4. The reaction mixture was stirred at the same temperature for 30 h. The resulting mixture was filtered and the solvent was removed by rotary evaporation at 30 - 40 °C to yield 8.20 g (ca. 100%) of the desired 1-phenylthio-3-chloropropene (*trans*:*cis* greater than 90:10). The product **36** was essentially pure and was stored at 0 °C and used without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.35 – 7.20 (m, 5 H), 6.49 (d, 1 H, J = 14.7 Hz), 5.77 (dt, 1 H, J_1 = 14.7 Hz, J_2 = 7.5 Hz), 4.06 (d, 2 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 133.4, 130.6, 129.7, 129.1, 127.4, 125.7, 44. These NMR data agreed well with the literature values.[58]

2-Methyl-1-phenylthio-3-chloropropene (37).

A 250 mL three-neck flask was charged at 5 °C with 3.7 mL of 2-methyl-3-(phenylthio)propene (**34**) (23.0 mmol), 4.57 g (34.3 mmol) of NCS and 50 mL of CCl_4. The reaction mixture was stirred at the same temperature for 30 h. The resulting mixture was filtered and the solvent was removed by rotary evaporation at 30 - 40 °C to yield 4.80 g (ca. 100%) of the desired 2-methyl-1-phenylthio-3-chloropropene. The product **37** was essentially pure and was stored at 0 °C and used without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.37-7.18 (m, 5 H), 6.34 (s, 1 H), 4.08 (s, 2 H), 1.91 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 135.2, 133.1, 129.4, 129.0, 126.7, 124.9, 50.5, 16.1.

Reaction of 37 with mono-*n*-butylzinc chloride (*n*-BuZnCl). 2-Methyl-3-phenylthio-1-heptene (37a).

A 1.6 M hexane solution of *n*-butyllithium (4.0 mL, 6.5 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 2-methyl-1-phenylthio-3-chloropropene **37** (1.20 g, 6.0 mmol) in 5 mL of THF. The reaction mixture was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and product was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to yield 1.17 g (88% yield) of 2-methyl-3-phenylthio-1-heptene (**37a**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.36 – 7.12 (m, 5 H), 4.66 (d, 1 H, J = 0.7 Hz), 4.59 (d, 1 H, J = 0.7 Hz), 3.61 (t, 1 H, J = 6.6 Hz), 1.75 (s, 3 H), 1.7 – 1.59 (m, 2 H), 1.35 – 1.30 (m, 4 H),

0.88 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 143.7, 135.6, 132.3, 128.4, 126.7, 113.4, 56.3, 32.2, 29.6, 22.3, 17.4, 13.9; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1288.

Reaction of 37 with mono-*sec*-butylzinc chloride (*sec*-BuZnCl). 2,4-Dimethyl-3-phenylthio-1-hexene (37b).

A 1.4 M hexane solution of *sec*-butyllithium (4.6 mL, 6.5 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 2-methyl-1-phenylthio-3-chloropropene **37** (1.20 g, 6.0 mmol) in 5 mL of THF. The reaction mixture was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and product was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to yield 1.20 g (91% yield) of 2,4-dimethyl-3-phenylthio-1-hexene (**37b –** a mixture of two diastereomers in a 1:1 ratio). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.34 – 7.10 (m, 5 H), 4.67 (m, 2 H), 3.45 – 3.39 (m, 1 H), 1.71 (s, 3 H); 1.13 (d, 3 H, J = 6.6 Hz), 0.96 – 0.85 (m, 5 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 143.1, 136.3, 136.1, 132.4, 132.2, 128.4, 126.6, 126.5, 114.0, 63.7, 63.3, 36.1, 35.8, 27.4, 26.9, 18.0, 17.6, 17.2, 17.0, 11.2, 10.7; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1283.

Reaction of 37 with mono-*t*-butylzinc chloride (*t*-BuZnCl). 2,4,4-Trimethyl-3-phenylthio-1-pentene (37c).

A 1.7 M hexane solution of *t*-butyllithium (3.8 mL, 6.5 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 2-methyl-1-phenylthio-3-chloropropene **37** (1.20 g, 6.0 mmol) in 5 mL of THF. The reaction mixture was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and product was extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to yield 1.25 g (93% yield) of 2,4,4-trimethyl-3-phenylthio-1-pentene (**37c**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.36 – 7.07 (m, 5 H), 4.72 (d, 1 H, J = 1.4 Hz), 4. 64 (d, 1 H, J = 1.4 Hz), 3.41 (s, 1 H), 1.81 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 143.8, 136.8, 132.0, 128.4, 126.4, 115.4, 69.2, 34.8, 28.8, 20.3; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1291.

(*E*)- and (*Z*)-Ethyl-3-phenylthio-2-butenoate (40).[59]

A solution of 5.33 g (95.0 mmol) of KOH was prepared in 150 mL of absolute EtOH and 9.6 mL (94.0 mmol) of PhSH was added during vigorous stirring in ambient conditions. The mixture was stirred for 30 min before the solution of 10.00 g (90.0 mmol) of ethyl butynoate-2 (**39**) in 20.0 mL of absolute EtOH was added. Stirring was continued for 24 h before an aqueous solution containing 10.0 g of glacial acetic was added. The product was extracted with ether (3×50 mL). The organic layers were combined, washed with 1 M aqueous NaOH and then with

brine. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel (10% ether/hexane) to give 14.0 g (70% yield) of the titled product **40** as a viscous oil (*cis:trans* ratio was 30:70). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.52 – 734 (m, 5 H), 5.85 (s, 0.3 H), 5.26 (s, 0.7 H), 4.21 (q, 0.6 H, *J* = 5.4 Hz), 4.05 (q, 1.4 H, *J* = 5.3 Hz), 2.43 (s, 2 H), 1.80 (s, 1 H), 1.29 (t, 1 H, *J* = 7.2 Hz), 1.19 (t, 2 H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 165.1, 159.5, 135.9, 135.3, 129.5, 128.8, 111.7, 110.7, 59.6, 59.3, 24.8, 19.8, 14.2, 14.1.

(*E*)- and (*Z*)-(3-phenylthio)-but-2-en-1-ol (41).

A 1.0 M dichloromethane solution of DIBAL (140 mL, 139 mmol) was added slowly to a solution of *E,Z*-ethyl-3-phenylthio-2-butenoate (**40**) (14.0 g, 63 mmol) in 120 mL of dichloromethane in an argon atmosphere at -78 °C. The reaction mixture was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl and the product was extracted with CH_2Cl_2 (5×100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to afford 10.9 g of the desired product **41** (96% yield of a crude product) as a colorless oil. The crude, but essentially pure, product **41** was used as is without further purification due to its potentially high chemical instability. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.28 – 7.20 (m, 5 H), 5.96 (t, 0.6 H, *J* = 5.4 Hz), 5.72 (t, 0.4 H, *J* = 5.4 Hz), 4.38 (d, 1.3 H, *J* = 6.6 Hz), 4.16 (d, 0.7 H, *J* = 6.6 Hz), 2.70 (s, broad, 1 H), 1.89 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 132.4, 132.3, 131.0, 129.0, 128.9, 128.6, 127.5, 126.8, 60.2, 59.1, 24.0, 17.7.

(*E*)- and (*Z*)-3-phenylthio-1-chloro-2-butene (42).

A solution of $SOCl_2$ (1.5 mL, 20.7 mmol) in 10 mL of ether was added dropwise to a solution of *E,Z*-(3-phenylthio)-but-2-en-1-ol (**41**) (3.54 g, 19.7 mmol) in 30 mL of diethyl ether in an argon atmosphere at 0 °C. The reaction mixture was stirred overnight at 0 °C and then quenched in saturated aqueous K_2CO_3 at 0 °C. The product was extracted with diethyl ether and the extract was dried over $MgSO_4$ and concentrated in vacuo to afford 3.50 g of the titled crude product (**42**) (90% yield), which was immediately used without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.36 – 7.22 (m, 5 H), 5.91 (t, 0.6 H, J = 7.5 Hz), 5.57 (t, 0.4 H, J = 8.1 Hz), 4.36 (d, 1.3 H, J = 7.5 Hz), 4.05 (d, 0.7 H, J = 8.1 Hz), 1.94 (s, 1 H), 1.89 (s, 2 H).

Undec-1-en-3-ol (47).

A solution of 3.0 mL (25.0 mmol) of nonanal (**44**) in 10 mL of dry diethyl ether was added dropwise to a solution of vinyllithium (42.0 mmol) in 180 mL of ether at -78 °C. The reaction mixture was stirred at -78 °C for 2 h, and then it was heated rapidly to -20 °C. The mixture was stirred at this temperature for 20 min. An aqueous saturated solution of K_2CO_3 was added to the reaction mixture at -20 °C. The product was extracted with diethyl ether (3×50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuo to yield a crude but the essentially pure titled product **47** (2.86 g, 68% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$), δ (ppm): 5.82 (ddd, 1 H, J_1 = 17.2 Hz, J_2 = 10.3 Hz, J_3 = 6.3 Hz), 5.20 (dd, 1 H, J_1 = 17.2 Hz, J_2 = 2.0 Hz), 5.08 (dd, 1 H, J_1 = 10.3 Hz, J_2 = 2.0 Hz), 4.09 – 4.03 (m, 1 H), 2.58 (s, 1 H), 1.39 – 1.95 (broad, 14 H), 0.86 (t, 3 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 141.3, 114.1, 73.0, 67.7, 36.9, 31.7, 29.5, 29.2, 25.2, 22.5, 13.9.

(*E*)-1-(3-chloroprop-1-enyl)-2-methylbenzene (49).

A solution of 3.2 mL (28.0 mmol) of *o*-tolualdehyde (**43**) in 10 mL of dry diethyl ether was added dropwise to a solution of vinyllithium (42.0 mmol) in 180 mL of ether at -78 °C. The reaction mixture was stirred at -78 °C for 2 h, and then it was heated rapidly to -20 °C. The mixture was stirred at this temperature for 20 min. Aqueous saturated solution of K_2CO_3 was added to the reaction mixture at -20 °C. The product was extracted with diethyl ether (3×50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuo to yield the crude product 1-o-tolylprop-2-en-1-ol (**46**) (4.17 g, ca 100% yield). The obtained product was immediately used without further purification.

A solution of 4.17 g (28.0 mmol) of crude **46** in 20 mL of diethyl ether was added to a solution of 3.57 g (30.0 mmol) of thionyl chloride in 60 mL of dry ether at ambient temperature in an argon atmosphere. The reaction mixture was stirred overnight at room temperature and the reaction was quenched with saturated aqueous K_2CO_3 at 0 °C. The product was extracted with diethyl ether and the extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel (10% EtOAc/hexane) to afford 3.1 g of the titled product (**49**) (67% yield from **43**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.38 – 7.07 (m, 4 H), 6.78 (d, 1 H, J = 14.0 Hz), 6.14 (dt, 1 H, J_1 = 14.0 Hz, J_2 = 7.1 Hz), 4.14 (d, 2 H, J = 7.1 Hz), 2.26 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 135.5, 134.7, 131.6, 130.2, 127.9, 126.4, 126.0, 125.7, 45.4, 19.0.

(*E*)-1-Chloroundec-2-ene (50).

A solution of 2.80 g (16.5 mmol) of crude **47** in 10 mL of diethyl ether was added to a solution of 2.10 g (17.2 mmol) of thionyl chloride in 50 mL of dry ether at ambient temperature in an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature and the

reaction was quenched with saturated aqueous K_2CO_3 at 0 °C. The product was extracted with diethyl ether. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over silica gel (100% hexane) to afford 1.7 g of the titled product (**50**) (55% of yield from **44**). ^{1}H NMR ($CDCl_3$), δ (ppm): 5.78 – 5.71 (m, 1 H), 5.64 – 5.56 (m, 1 H), 4.01 (d, 2 H, *J* = 7.0 Hz), 2.06 (m, 2 H), 1.40 – 1.27 (broad, 12 H), 0.86 (t, 3 H, *J* = 5.1 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 136.0, 125.9, 45.2, 32.0, 31.8, 29.4, 29.2, 29.1, 28.8, 22.6, 14.0; exact mass calcd. for $C_{11}H_{21}Cl$ 188.1332, found 188.1326.

(*E*)-1-chloro-4-methylhept-2-ene (51).

A solution of 36.0 mL (0.300 mol) of 2-methylvaleraldehyde (**45**) in 20 mL of dry THF was added in 1 h using a syringe pump to a mixture of a 1.0 M solution of vinylmagnesium bromide in THF (200.0 mL, 0.200 mol) and a 1.6 M solution of vinylmagnesium chloride in THF (100.0 mL, 0.160 mol) at 0 °C. The reaction mixture was stirred overnight at room temperature and the reaction was quenched with saturated aqueous K_2CO_3. The product was extracted with diethyl ether (3×50 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated in vacuo to yield a crude, but the essentially pure, product 4-methylhept-1-en-3-ol (**48**) (35.0 g, 91% yield). The obtained crude product was used without further purification.

A solution of 26.3 g (0.205 mol) of crude **48** in 25 mL of diethyl ether was added dropwise using a syringe pump to a solution of 29.8 g (0.250 mol) of thionyl chloride in 250 mL of dry ether at 0 °C in an argon atmosphere. The reaction mixture was stirred for 24 h at room temperature and the reaction was quenched with saturated aqueous K_2CO_3 at 0 °C. The product was extracted with diethyl ether. The extract was dried over $MgSO_4$ and concentrated in vacuo

at 35 °C. The residue was chromatographed over silica gel (100% pentane) to afford 23.2 g of the titled product **51** (80% yield). ^{1}H NMR ($CDCl_3$), δ (ppm): 5.63 – 5.51 (m, 2 H), 4.02 (d, 2 H, J = 6.2 Hz), 2.21 – 2.12 (m, 1 H), 1.35 – 1.25 (m, 4 H), 0.98 (d, 3 H, J = 8.2 Hz), 0.80 (t, 3 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 141.6, 124.2, 45.4, 38.8, 36.0, 20.2, 20.0, 14.0; exact mass calcd. for $C_8H_{15}Cl$ 146.0862, found 146.0858.

(*E*)-Ethyl 4-methylhept-2-enoate (52).

A 250 mL three neck round bottom flask was purged three times with argon gas and charged with 8.5 mL (71.5 mmol) of 2-methylvaleraldehyde (**45**) and 120 mL of dry dichloromethane. (Carbethoxymethylene)triphenylphosphorane (25.00 g, 71.8 mmol) was added in one portion under vigorous argon flow. The reaction mixture was heated at reflux and allowed to stir overnight. Then it was cooled to ambient temperature and the solvent was removed in vacuo. The crude residue was taken up in a minimum amount of dichloromethane and then diluted with pentane until precipitation ceased. The mixture was cooled to 0 °C and then filtered. The organic solvents were removed in vacuo. The residue was dissolved in 50 mL of dry pentane and the solution was cooled again to 0 °C. The formed precipitate was filtered off and pentane was rotary evaporated to give 12.0 g (98% yield) of crude, but essentially pure, *E*-ethyl 4-methylhept-2-enoate (**52**). ^{1}H NMR ($CDCl_3$), δ (ppm): 6.86 (dd, 1 H, J_1 = 15.6 Hz, J_2 = 7.8 Hz), 5.77 (d, 1 H, J = 15.6 Hz), 4.18 (q, 2 H, J = 7.2 Hz), 2.34 – 2.27 (m, 1 H), 1.38 – 1.26 (m, 7 H), 1.04 (d, 3 H, J = 6.6 Hz), 0.75 (t, 3 H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 166.6, 154.3, 119.4, 59.8, 38.0, 36.0, 20.1, 19.1, 14.0, 13.8; exact mass calcd. for $C_{10}H_{18}O_2$ 170.1307, found 170.1303.

(*E*)-4-methylhept-2-en-1-ol (53).

A 500 mL three neck round bottom flask was purged 3 times with argon gas and charged with crude *E*-ethyl 4-methylhept-2-enoate (**52**) (12.0 g, 70 mmol) and 200 mL of dry dichloromethane. A 1.0 M solution of DIBAL (154 mL, 154 mmol) was slowly added at -78 °C. The reaction mixture was stirred and allowed to warm slowly to the room temperature overnight. Then the reaction was quenched with saturated aqueous NH_4Cl. The product was extracted with dichloromethane and then washed with brine. The extract was dried over $MgSO_4$ and concentrated in vacuo to afford 9.83 g (98% yield) of crude, but essentially pure, allylic alcohol **53**. Due to high chemical instability on regular silica gel, the observed product **53** was used immediately without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 5.55 – 5.52 (m, 2 H), 4.05 – 3.95 (s, broad, 2 H), 2.32 – 2.25 (s, broad, 1 H), 2.13 – 2.09 (m, 1 H), 1.30 – 1.23 (m, 4 H), 0.95 (d, 3 H, J = 6.0 Hz), 0.84 (t, 3 H, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 138.5, 127.0, 63.2, 38.9, 35.3, 20.4, 20.2, 13.9.

3-Chloro-4-methylhept-1-ene (54).

A 250 mL flask was purged three times with argon gas and charged with 2.20 g (17.2 mmol) of *E*-4-methylhept-2-en-1-ol (**53**), 2.1 mL (25.8 mmol) of methyl imidazole and 100 mL of dry Et_2O. A solution 2.50 g (21.0 mmol) of $SOCl_2$ in 10 mL of dry ether was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 24 h and the reaction was quenched at this temperature with saturated aqueous K_2CO_3. The product was extracted with ether and then washed with 200 mL of deionized water. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over basic alumina (100% hexane) to afford 1.51 g (60% yield) of 3-chloro-4-methylhept-1-ene (**54**, two diastereomers). ^{1}H NMR ($CDCl_3$), δ

(ppm): 6.01 – 5.88 (m, 1 H), 5.35 – 5.14 (m, 2 H), 4.43 – 4.31 (m, 1 H), 1.95 – 1.75, (m 1 H), 1.60 – 1.15 (broad, 4 H), 1.04 – 0.84 (m, 6 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 137.4, 136.5, 117.2, 116.7, 68.6, 68.5, 39.6, 39.3, 35.7, 35.3, 20.1, 20.0, 15.7, 15.1.

Diethyl 4-methylhept-1-en-3-yl phosphate (56).

To a 0 °C solution of 5.40 g (42.3 mmol) of 4-methylhept-1-en-3-ol (**48**) in 100 mL of dry ether was added via syringe a 1.6 M solution of *n*-butyllithium (28.6 mL, 42.3 mmol). After the solution had been stirred for 1 h at 0 °C, 6.4 mL (44.3 mmol) of diethyl chlorophosphate was added dropwise. The solution was stirred for 1 h at 0 °C and for 24 h at ambient temperature. Then the reaction was quenched with saturated aqueous K_2CO_3. The product was extracted with ether and washed with brine. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (50% EtOAc/hexane) to afford 9.1 g (93% yield) of the desired product **56** (two diastereomers). ^{1}H NMR ($CDCl_3$), δ (ppm): 5.66 – 5.57 (m, 1 H), 5.13 – 5.01 (m, 2 H), 4.48 – 4.35 (m, 1 H), 3.94 – 3.81 (m, 4 H), 1.70 – 1.42 (m, 1 H), 1.33 – 1.08 (broad, 10 H), 0.74 – 0.63 (m, 6 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 135.0, 134.1, 117.7, 117.2, 83.0, 82.9, 63.0, 62.9, 37.5, 37.2, 33.9, 33.4, 19.7, 19.6, 15.7, 15.6, 14.1, 13.9, 13.6, 13.5; exact mass calcd. for ($C_{12}H_{25}O_4P$ + Na) 287.1388, found 288.1383.

Diethyl oct-1-en-3-yl phosphate (57).

To a 0 °C solution of 5.0 mL (32.6 mmol) of oct-1-en-2-ol (**55**) in 50 mL of dry ether was added via syringe a 1.6 M solution of *n*-butyllithium (22.0 mL, 34.3 mmol). After the solution had been stirred for 1 h at 0 °C, 5.0 mL (34.3 mmol) of diethyl chlorophosphate was added dropwise. The solution was stirred for 1 h at 0 °C and for 16 h at ambient temperature. Then the

reaction was quenched with saturated aqueous K_2CO_3. The product was extracted with ether and washed with brine. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (50% EtOAc/hexane) to afford 7.3 g (97% yield) of the desired product **57**. ^{1}H NMR ($CDCl_3$), δ (ppm): 5.84 (ddd, 1 H, J_1 = 18.0 Hz, J_2 = 9.0 Hz, J_3 = 6.0 Hz), 5.31 (d, 1 H, J = 18.0 Hz), 5.20 (d, 1 H, J = 12.0 Hz), 4.79 – 4.68 (m, 1 H), 4.11 (q, 4 H, J = 6.0 Hz), 1.75 – 156 (m, 2 H), 1.39 – 129 (m, 12 H), 0.89 (t, 3 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 13.7, 116.6, 79.4, 63.1, 35.4, 31.1, 24.0, 22.1, 15.7, 14.6; exact mass calcd. for $C_{12}H_{25}O_4P$ 264.1490, found 264.1488.

Reaction of 36 with *n*-butylzinc chloride (*n*-BuZnCl). High concentration of the organozinc reagent. 3-Phenylthio-1-heptene (58a).

A 1.6 M hexane solution of *n*-butyllithium (4.0 mL, 6.5 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.08 g) was added in one portion followed by dropwise addition of a solution of 1-phenylthio-3-chloropropene **36** (1.00 g, 5.4 mmol) in 5 mL of THF. The reaction mixture was stirred for 1 h at -78 °C and then it was allowed to slowly warm to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to yield 1.00 g (92% yield) of 3-phenylthio-1-heptene (**58a**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.36 – 7.11 (m, 5 H), 5.64 (m, 1 H), 4.87 (d, 1 H, J = 10.0 Hz), 4.81 (d, 1 H, J = 17.0 Hz), 3.54 (m, 1 H), 1.62 (m, 2 H), 1.42 – 1.25 (m, 4 H), 0.87 (t, 3 H, J = 7.1 Hz) ; ^{13}C NMR

($CDCl_3$), δ (ppm): 138.7, 134.7, 132.4, 128.3, 126.6, 115.1, 52.0, 33.6, 29.1, 22.2, 13.7; exact mass calcd. for $C_{13}H_{18}S$ 206.1129, found 206.1123.

Reaction of 36 with a half equiv of di-*n*-butylzinc (*n*-Bu_2Zn). High concentration of the organozinc reagent. 3-Phenylthio-1-heptene (58a).

A 1.6 M hexane solution of *n*-butyllithium (4.0 mL, 6.5 mmol, 1.2 equiv) and a 0.5 M THF solution of $ZnCl_2$ (6.6 mL, 3.3 mmol, 0.60 equiv) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 was added (~5 mol %, 0.04 g) in one portion followed by dropwise addition of a solution of 1-phenylthio-3-chloropropene **36** (1.00 g, 5.4 mmol, 1.00 equiv) in 5 mL of THF. The reaction mixture was stirred for 1 h at -78 °C and then it was allowed to slowly warm to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and the product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to yield 1.10 g (97% yield) of essentially pure 3-phenylthio-1-heptene (**58a**). The ^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) spectra and elemental analysis of (**58a**) are given above.

Reaction of 36 with *n*-butylzinc thiophenoxy cuprate (*n*-BuCu(SPh)ZnCl). 3-Phenylthio-1-heptene (58a).

A stirred suspension of CuBr•SMe_2 (0.67 g, 3.3 mmol) in THF (8 mL) was treated at 25 °C with a 1.0 M THF solution of lithium thiophenoxide (3.30 mL, 3.3 mmol). A clear bright yellow solution was formed in 5 min but became a cloudy suspension upon cooling to -78 °C.

Dropwise addition of a 1.6 M hexane solution of *n*-butyllithium (2.0 mL, 3.2 mmol) to a cold suspension at -78 °C gave a fine, nearly white precipitate. After 10 min, a 0.5 M THF solution of $ZnCl_2$ (6.5 mL, 3.3 mmol) was added at -78 °C. The resulting mixture was stirred for 1 h and then 5 mL of a precooled solution containing 1-phenythio-3-chloropropene **36** (0.50 g, 2.7 mmol) in THF was injected. The solution was allowed to slowly warm to room temperature and the reaction was quenched with 200 mL of aqueous K_2CO_3. The yellow precipitate formed was removed by filtration through a celite pad. The product was extracted with diethyl ether (3×50 mL). The combined organic extract was washed with a 1 M aqueous solution of NaOH and then with brine. The extract was dried over $MgSO_4$ and the organic solvents were removed by rotory evaporation. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to yield 0.51 g (92% yield) of crude 3-phenylthio-1-heptene (**58a**). The ^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) spectra and elemental analysis of (**58a**) are given above.

Reaction of 36 with *tert*-butylzinc chloride (*t*-BuZnCl). High concentration of the organozinc reagent. 4,4-Dimethyl-3-phenylthio-1-pentene (58b).

A 1.7 M pentane solution of *t*-butyllithium (3.8 mL, 6.5 mmol, 1.2 equiv) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol, 1.2 equiv) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 was added (~5 mol%, 0.08 g) in one portion followed by dropwise addition of a solution of 1-phenylthio-3-chloropropene **36** (1.00 g, 5.4 mmol, 1.00 equiv) in 5 mL of THF. The mixture was stirred for 1 h at -78 °C and then it was allowed to slowly warm to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and the product was extracted with diethyl ether. The extract was washed with brine and then dried

over $MgSO_4$. The organic solvents were removed under reduced pressure. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 1.08 g (97% yield) of 4,4-dimethyl-3-phenylthio-1-pentene (**58b**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.35 – 7.03 (m, 5 H), 5.75 (m, 1 H), 4.80 (d, 1 H, *J* = 10.0 Hz), 4.60 (d, 1 H, *J* = 16.0 Hz), 3.24 (d, 1 H, *J* = 10.0 Hz), 1.08 (s, 9.0 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 136.3, 135.6, 132.7, 128.5, 126.5, 115.3, 65.8, 34.0, 27.8. exact mass calcd. for $C_{13}H_{18}S$ 206.1129, found 206.1135.

Reaction of 36 with a half equivalent of di-*tert*-butylzinc (*t*-Bu_2Zn). 4,4-Dimethyl-3-phenylthio-1-pentene (58b).

A 1.7 M pentane solution of *t*-butyllithium (3.8 mL, 6.5 mmol, 1.2 equiv) and a 0.5 M THF solution of $ZnCl_2$ (6.6 mL, 3.3 mmol, 0.6 equiv) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 was added (~5 mol%, 0.04 g) in one portion followed by dropwise addition of a solution of 1-phenylthio-3-chloropropene **36** (1.00 g, 5.4 mmol, 1.00 equiv) in 5mL of THF. The reaction mixture was stirred for 1 h at -78 °C and then it was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and the product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The crude residue was chromatographed on silica gel (2.5% EtOAc/hexane) to afford 1.07 g (98% yield) of 4,4-dimethyl-3-phenylthio-1-pentene (**58b**). The ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) spectra and elemental analysis of (**58b**) are given above.

Reaction of 36 with *tert*-butylzinc chloro phenylthio cuprate [*t*-BuCu(SPh)]ZnCl in the presence of $[I]^-$ ion. 4,4-Dimethyl-3-phenylthio-1-pentene (58b).

A stirred suspension of CuI (0.62 g, 3.2 mmol) in THF (8 mL) was treated at 25 °C with a 1.0 M THF solution of lithium thiophenoxide (3.2 mL, 3.2 mmol). A clear bright yellow solution was formed in 5 min but became a cloudy suspension upon cooling to -78 °C. Dropwise addition of a 1.7 M pentane solution of *t*-butyllithium (1.9 mL, 3.2 mmol) to the cold suspension at -78 °C gave a fine, nearly white precipitate. After 10 min a 0.5 M THF solution of $ZnCl_2$ (6.5 mL, 3.3 mmol) was added at -78 °C. The resulting mixture was stirred for 1 h and then 5 mL of a precooled solution containing 1-phenythio-3-chloropropene **36** (0.50 g, 2.7 mmol) in THF was injected. The solution was allowed to slowly warm to room temperature and was quenched with 200 mL of saturated aq. NH_4Cl. The yellow precipitate that formed was removed by filtration through a celite pad. The filtrate was extracted with diethyl ether. The combined organic layers were washed with a 1 M solution of NaOH and then with brine. The extract was dried over $MgSO_4$ and the organic solvents were removed by rotary evaporation. The NMR spectra of the crude product indicated the formation of a mixture consisting of ca. 31% of 4,4-dimethyl-3-phenylthio-1-pentene **58b** and ca. 64% of 1,3-bis(phenylthio)propene **82**. The crude material was passed through a short silica gel column and the products were separated and eluted with 5% EtOAc in hexane. The ^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) spectra and elemental analysis of 4,4-dimethyl-3-phenylthio-1-pentene **58b** are given above.

Reaction of an allyl chloride with a monoalkylzinc chloride (RZnCl) under general conditions (A).

An oven-dried 100 mL three-neck round bottom flask was purged three times with argon gas, charged with 20 mL of dry THF and cooled to -78 °C. A hexane or pentane solution of an alkyllithium (6.5 mmol) was added slowly at -78 °C followed by dropwise addition of a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) at the same temperature. The resulting mixture was stirred at -78 °C for 40 min and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of the corresponding allyl chloride (5.4 mmol) in 5 mL of THF. The reaction mixture was stirred and allowed to warm slowly to the room temperature overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution. The organic material was extracted with ether (3×50 mL) and the combined organic layers were washed with brine and then dried over anhydrous $MgSO_4$. The organic solvents were removed by rotary evaporation and the crude residue was chromatographed over silica gel (100% hexanes) to afford the substitution product as a colorless oil.

Reaction of an allyl chloride with a monoalkylzinc chloride (RZnCl) under general conditions (B).

An oven-dried 100 mL three-neck round bottom flask was purged three times with argon gas, charged with 20 mL of dry THF and cooled to -78 °C. A hexane or pentane solution of an alkyllithium (6.5 mmol) was added slowly at -78 °C followed by dropwise addition of a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) at the same temperature. After being stirred at -78 °C for 40 min, the resulting mixture was warmed to -70 °C. CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion at -70 °C followed by dropwise addition of a solution of the corresponding

allyl chloride (5.4 mmol) in 5 mL of THF at the current temperature. The reaction mixture was stirred at -70 °C for 24 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. The organic products were extracted with ether and the extract was washed with brine. The extract was dried over anhydrous $MgSO_4$ and the organic solvents were removed by rotary evaporation. The crude residue was chromatographed over silica gel (100% hexanes) to afford the substitution product as a colorless oil.

Reaction of an allyl chloride with a monoalkylzinc chloride (RZnCl) under general conditions (C).

An oven-dried 100 mL three-neck round bottom flask was purged three times with argon gas and charged with 20 mL of dry THF and the mixture was cooled to -78 °C. A hexane or pentane solution of an alkyllithium (6.5 mmol) was added slowly at -78 °C followed by dropwise addition of a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) at the same temperature. After being stirred at -78 °C for 40 min, the resulting mixture was warmed quickly to room temperature and then cooled to 0 °C. $CuBr•SMe_2$ (~5 mol%, 0.07 g) was added in one portion at 0 °C followed by dropwise addition of a solution of an allyl chloride (5.4 mmol) in 5 mL of THF at that temperature. The reaction mixture was stirred at 0 °C overnight. The reaction was quenched with a saturated aqueous NH_4Cl solution. The organic products were extracted with ether and the extract was washed with brine. The extract was dried over anhydrous $MgSO_4$ and the organic solvents were removed by rotary evaporation. The crude residue was chromatographed over silica gel (100% hexanes) to afford the substitution product as a colorless oil.

Reaction of an allyl chloride with a monoalkylzinc chloride (RZnCl) catalyzed by 1 equiv of CuSPh.

An oven-dried 100 mL three-neck round bottom flask was purged three times with argon gas, charged with 30 mL of dry THF and cooled to -78 °C. A hexane or pentane solution of an alkyllithium (6.5 mmol) was added slowly at -78 °C followed by dropwise addition of a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) at the same temperature. After being stirred at -78 °C for 40 min, the resulting mixture was heated quickly to room temperature. CuSPh (1.12 g, 6.5 mmol) was added in one portion followed by dropwise addition of a solution of the corresponding allyl chloride (5.4 mmol) in 5 mL of THF. The reaction mixture was stirred at room temperature for 30 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was filtered though a celite pad and the organic products were extracted with ether and the extract was washed with brine. The extract was dried over anhydrous $MgSO_4$ and the organic solvents were removed by rotary evaporation. The crude residue was chromatographed over silica gel (100% hexanes) to afford the substitution product as a colorless oil.

3-*n*-Butyl-1-undecene (60) was produced in general conditions (A) in 92% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.59-5.47 (m, 1 H), 4.94 (s, 1H), 4.89 (dd, 1 H, J_1 = 9.1 Hz, J_2 = 1.8 Hz), 2.03-1.86 (m, 1 H), 1.47-1.08 (broad, 20 H), 0.88 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 143.7, 113.8, 44.2, 35.2, 34.9, 32.0, 29.9, 29.74, 29.47, 27.3, 22.9, 22.8, 14.1; exact mass calcd. for $C_{15}H_{30}$ 210.2348, found 210.2353.

3-*sec*-Butyl-1-undecene – two diastereomers (61) was produced in general conditions (A) in 90% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.63-5.49 (m, 1 H), 5.00-4.88 (m, 2 H), 1.96-1.78 (broad, 2 H), 1.49-1.13 (broad, 16 H), 0.90-0.79 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 141.9, 140.5, 115.1, 114.7, 49.6, 48.3, 38.9, 38.5, 32.6, 32.1, 31.1, 30.0, 29.8, 29.5, 27.8, 26.1, 22.8, 16.5, 15.1, 14.1, 11.9, 11.8; exact mass calcd. for $C_{15}H_{30}$ 210.2348, found 210.2343.

3-*tert*-Butyl-1-undecene (62) was produced in general conditions (A) in 98% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.53 (ddd, 1 H, J_1 = 17.0 Hz, J_2 = 10.1 Hz, J_3 = 7.0 Hz), 5.00 (dd, 1 H, J_1 = 10.1 Hz, J_2 = 2.4 Hz), 4.89 (dd, 1 H, J_1 = 17.0 Hz, J_2 = 2.4 Hz), 1.92 (m, 1 H), 1.45-1.10 (broad, 12 H), 1.05 (m, 2 H), 0.93-0.85 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 140.6, 115.7, 55.3, 32.5, 32.0, 29.8, 29.5, 29.3, 28.7, 28.3, 27.8, 22.8, 14.2; exact mass calcd. for $C_{15}H_{30}$ 210.2348, found 210.2343.

3-Phenyl-1-heptene (63) was produced in general conditions (A) in 92% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.27-7.11 (m, 5 H), 5.98-5.87 (m, 1 H), 5.03 – 4.96 (m, 2H), 3.20 (m, 1 H), 1.69 (dt, 2 H, J_1 = 7.3 Hz, J_2 = 5.2 Hz), 1.32-1.20 (broad, 4 H), 0.85 (t, 3 H, J = 7.1); ^{13}C NMR ($CDCl_3$) δ (ppm): 144.6, 142.5, 128.4, 127.6, 126.0, 113.7, 49.9, 35.2, 29.7, 22.7, 14.0.

4-Methyl-3-phenyl-1-hexene (64) was produced in general conditions (A) in 91% yield as a colorless oil (two diastereomers): ^{1}H NMR ($CDCl_3$) δ (ppm): 7.35-7.14 (m, 5 H), 6.04-5.92 (m, 1 H), 5.05-4.99 (m, 2 H), 3.06-2.97 (m, 1 H), 1.82-1.68 (m, 1 H), 0.97-0.71 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 144.3, 144.1, 141.3, 140.7, 128.3, 128.0, 127.8, 125.9, 115.1, 114.8, 56.8,

56.4, 39.0 (2C), 27.1, 26.8, 16.8, 16.5, 11.3, 11.2; exact mass calcd. for $C_{13}H_{18}$ 174.1409, found 174.1409.

4,4-Dimethyl-3-phenyl-1-pentene (65) was produced in general conditions (C) in 91% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.27-7.14 (m, 5 H), 6.25 (ddd, 1 H, J_1 = 16.8 Hz , J_2 = 9.8 Hz, J_3 = 6.9 Hz), 5.08-5.0 (m, 2 H), 3.01 (d, 1 H, J = 9.8), 0.89 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 142.7, 138.8, 129.1, 127.7, 126.0, 116.2, 61.6, 33.8, 28.0; exact mass calcd. for $C_{13}H_{18}$ 174.1409, found 174.1408.

4,4-Dimethyl-1-phenylthio-1-pentene (66) was produced in general conditions (B) in 67% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.34 – 7.12 (m, 5 H), 6.31 – 6.21 (m, 2 H), 2.06 (d, 2 H, J = 6.8 Hz), 0.93, (s, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 137.9, 131.9, 128.4, 128.0, 126.8, 126.0, 47.6, 31.4, 29.4.

3-*o*-Tolyl-1-heptene (67) was produced in general conditions (A) in 96% yield as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.17-7.07 (m, 4 H), 5.86 (ddd, 1 H, J_1 = 17.0 Hz, J_2 = 10.3 Hz, J_3 = 7.4 Hz), 5.00-4.92 (m, 2 H), 3.47 (dt, 1 H, J_1 = 7.4 Hz, J_2 = 7.4 Hz), 2.31 (s, 3 H), 1.71-1.68 (m, 2 H), 1.33-1.27 (m, 4 H), 0.87 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 142.4, 142.0, 135.7, 130.3, 126.5, 126.3, 125.7, 113.7, 45.0, 34.8, 29.8, 22.8, 19.7, 14.0; exact mass calcd. for $C_{14}H_{20}$ 188.1565, found 188.1566.

4-Methyl-3-*o*-tolyl-1-hexene - two diastereomers (68) was produced in general conditions (A) in 93% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.13-7.02 (m, 4 H), 5.93-5.81 (m, 1

H), 4.99-4.92 (m, 2 H), 3.28-3.20 (m, 1 H), 2.29 (s, 3 H), 1.75-1.71 (m, 1 H), 0.97-0.88 (m, 2 H), 0.79 (t, 3 H, J = 7.3), 0.70 (d, 3 H, J = 6.6); ^{13}C NMR ($CDCl_3$) δ (ppm): 142.4, 142.3, 141.4, 140.9, 135.6, 130.4, 126.6, 126.0, 125.5, 114.6, 114.5, 51.8, 51.6, 38.6, 38.3, 27.0, 26.9, 19.9, 19.8, 16.8, 16.6,11.4, 11.1; exact mass calcd. for $C_{14}H_{20}$ 188.1565, found 188.1569.

4,4-Dimethyl-3-*o*-tolyl-1-pentene (69) was produced in general conditions (C) in 98% yield as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.21-7.03 (m, 4 H), 6.16 (ddd, 1 H, J_1 = 16.7 Hz, J_2 = 10.1 Hz, J_3 = 7.6 Hz), 5.03-4.94 (m, 2 H), 3.42 (d, 1 H, J = 7.6 Hz), 2.33 (s, 3 H), 0.92 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 141.2, 139.6, 136.1, 130.5, 128.2, 125.6, 125.3, 115.8, 54.7, 34.9, 28.0, 20.9; exact mass calcd. for $C_{14}H_{20}$ 188.1565, found 188.1562.

4,4-Dimethyl-1-*o*-tolyl-1-pentene (70) was produced in general conditions (B) in 76% yield as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.40 (d, 1 H, J = 5.9 Hz), 7.17 – 7.10 (m, 3 H), 6.53 (d, 1 H, J = 15.6 Hz), 6.10 (td, 1 H, J_1 = 15.5 Hz, J_2 = 7.6 Hz), 2.26 (s, 3 H), 2.10 (d, 2 H, J = 7.6 Hz), 0.95 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 137.2, 134.7, 130.1, 129.4, 126.8, 126.0, 125.7, 47.9, 31.2, 29.4, 19.8; exact mass calcd. for $C_{14}H_{20}$ 188.1565, found 188.1573.

6-*n*-Butyl-2,6-dimethyl-2,7-octadiene (71) was produced in general conditions (A) in quantitative yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.68 (dd, 1 H, J_1 = 17.5 Hz, J_2 = 10.8 Hz), 5.08 (t, 1 H, J = 6.5 Hz), 4.96 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 1.5 Hz), 4.90 (dd, 1 H, J_1 = 17.5 Hz, J_2 = 1.5 Hz), 1.91-1.83 (m, 2 H), 1.66 (s, 3 H), 1.57 (s, 3 H), 1.31-1.21 (br, 8 H), 0.94 (s, 3 H), 0.88 (t, 3 H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ (ppm): 147.4, 130.7, 125.2, 124.9,

111.4, 40.9, 40.7, 39.9, 39.4, 26.3, 25.7, 23.6, 22.9, 22.5, 17.5, 14.6. These NMR data agreed well with the literature values.[60] Exact mass calcd. for $C_{14}H_{26}$ 194.2035, found 194.2038.

2-*sec*-Butyl-2,6,-dimethyl-2,7-octadiene - two diastereomers (72) was produced in general conditions (A) in 94% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.74-5.61 (m, 1 H), 5.09-4.99 (m, 2 H), 4.92-4.84 (m, 1 H), 2.07-1.93 (m, 1 H), 1.89-1.81(m, 2 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.36-1.22 (m, 2 H), 0.91-0.78 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 146.5, 146.4, 130.7, 125.3, 112.2, 111.9, 42.9, 42.6, 39.4, 38.9, 25.7, 24.5, 23.8, 22.9, 18.3, 17.9, 17.5, 13.8, 13.2, 13.0; exact mass calcd. for $C_{14}H_{26}$ 194.2035, found 194.2028.

(*E*)-2,6,9-Trimethyl-2,6-undecadiene (73) was produced by the reaction with 1 equiv of *s*-Bu_2Zn catalyzed by CuBr•SMe_2 in general conditions (A) and (B) in quantitative yields as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.14-5.08 (m, 2 H), 2.09-1.96 (m, 4 H), 1.84-1.75 (m, 2 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.39-1.33 (m, 2 H), 1.18-1.06 (m, 1 H), 0.90-0.84 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 135.2, 131.1, 124.5, 123.6, 40.0, 35.5, 35.0, 29.3, 26.8, 25.7, 19.1, 17.6, 16.0, 11.6; exact mass calcd. for $C_{14}H_{26}$ 194.2035, found 194.2040.

(*E*) and (*Z*)-2,6,9,9-Tetramethyl-2,6-decadiene (74) was produced in general conditions (C) in 86% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.20 (t, 1 H, J = 7.7 Hz), 5.10 (t, 1 H, J = 6.5 Hz), 2.10 (m, 4 H), 1.87 (d, 2 H, J = 7.7 Hz), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 0.87 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 136.0, 135.9, 131.1, 130.9, 124.6, 122.4, 122.0, 42.0, 41.8, 40.2, 32.0, 31.7, 29.3, 26.8, 25.7, 17.6, 16.0; exact mass calcd. for $C_{14}H_{26}$ 194.2035, found 194.2037.

(*E*)-3-Butyl-4-methyl-1-heptene (75) was produced by CuBr•SMe_2 catalysis in general conditions (A) and (C), and by CuSPh catalysis in 72%, 96% and 90% yield respectively (in a mixture with 12 – 13% of the α-S_{AL} product) as a colorless oil (two diastereomers): ^{1}H NMR ($CDCl_3$) δ (ppm): 5.67 – 5.55 (m, 1 H), 5.05 – 4.93 (m, 2 H), 2.03 – 1.88 (m, 1 H), 1.53 – 1.12 (broad, 11 H), 0.95 – 0.84 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 141.8, 140.5, 115.1, 114.8, 49.8, 48.6, 37.5, 36.9, 36.6, 35.7, 32.7, 32.3, 30.8, 30.1, 23.0, 22.7, 20.5, 20.4, 17.1, 15.4, 14.2, 14.0; exact mass calcd. for $C_{12}H_{24}$ 168.1878, found 168.1876.

(*E*)-3-*t*-Butyl-4-methyl-1-heptene (76) was produced in general conditions (C) in 94% yield (in a mixture with 12% of the α-S_{AL} product **76**) as a colorless oil (two diastereomers): ^{1}H NMR ($CDCl_3$) δ (ppm): 5.76 (m, 1 H), 5.06 (dd, 1 H, J_1 = 10.0 Hz, J_2 = 2.7 Hz), 4.91 (dd, 1 H, J_1 = 16.8 Hz, J_2 = 2.7 Hz), 1.82 – 1.77 (m, 1 H), 1.56 – 1.48 (m, 1 H), 1.38 – 1.14 (broad, 4 H), 1.00 – 0.84 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 137.6, 137.5, 116.4, 116.3, 61.2, 58.3, 40.5, 39.6, 32.4, 31.8, 29.3, 28.7, 20.6, 20.5, 17.0, 14.5, 14.4; exact mass calcd. for $C_{12}H_{24}$ 168.1878, found 168.1873.

(*E*)-2,2,6-Trimethyl-4-nonene (77) was produced in general conditions (A) with 4-methyl-3-chloro-1-heptene (**54**) or with diethyl 4-methylhept-1-en-3-yl phosphate (**56**) as a substrate in 98% and 100% yield respectively as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.48 – 5.39 (m, 1 H), 5.27 (dd, 1 H, J_1 = 15.0 Hz, J_2 = 6.0 Hz), 2.19 – 2.10 (m, 1 H), 1.91 (d, 2 H, J = 6.0 Hz), 1.41 – 1.21 (broad, 4 H), 0.99 (d, 3 H, J = 6.0 Hz), 0.96 – 0.89 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 139.0, 125.4, 47.3, 39.7, 36.9, 31.0, 29.4, 21.2, 20.7, 14.3; exact mass calcd. for $C_{12}H_{24}$ 168.1878, found 168.1873.

(*E*)-4-Methyl-5-undecene (78) was produced in general conditions (A) with 4-methyl-3-chloro-1-heptene (**54**) or with diethyl 4-methylhept-1-en-3-yl phosphate (**56**) as a substrate in 97% and 100% yield respectively as a colorless oil (predominantly *E*-isomer): ^{1}H NMR ($CDCl_3$) δ (ppm): 5.44 – 5.24 (m, 2 H), 2.15 – 1.98 (m, 3 H), 1.42 – 1.26 (broad, 10 H), 1.04 – 0.90 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 136.5, 128.5, 39.7, 36.6, 32.7, 31.5, 29.6, 22.7, 21.0, 20.5, 14.2, 14.1; exact mass calcd. for $C_{12}H_{24}$ 168.1878, found 168.1879.

(*E*)-6-Dodecene (79) was produced in general conditions (A) in 91% yield as a colorless oil (predominantly *E*-isomer): ^{1}H NMR ($CDCl_3$) δ (ppm): 5.38 (t, 2 H, J = 3.0 Hz), 1.98 – 1.94 (m, 4 H), 1.40 – 1.22 (broad, 12 H), 0.88 (t, 6 H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 130.1, 32.8, 31.6, 29.5, 27.3, 22.7, 14.1; exact mass calcd. for $C_{12}H_{24}$ 168.1878, found 168.1879.

(*E*)- and (*Z*)-2,2-Dimethyl-4-decene (80) was produced in general conditions (A) in 97% yield as a colorless oil (*E*/Z 2:1): ^{1}H NMR ($CDCl_3$) δ (ppm): 5.49 – 5.42 (m, 2 H), 2.08 – 1.90 (m, 4 H), 1.44 – 1.32 (broad, 6 H), 0.95 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ (ppm): ; exact mass calcd. for $C_{12}H_{24}$ 168.1878, found 168.1876.

3-Methyl-3-phenylthio-1-heptene (82a).

A 1.6 M hexane solution of *n*-butyllithium (4.1 mL, 6.6 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.5 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 1-methyl-1-phenylthio-3-chloropropene **42** (1.00 g, 5.0 mmol) in 5 mL of THF. The reaction mixture was stirred for 1 h

at -78 °C and then it was allowed to warm slowly to room temperature for 16 h. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 0.97 g (88%) of 3-methyl-3-phenylthio-1-heptene (**82a**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.46 – 7.22 (m, 5 H), 5.88 (dd, 1 H, J_1 = 18.0 Hz, J_2 = 12.0 Hz), 4.93 (d, 1 H, J = 12.0 Hz), 4.65 (d, 1 H, J = 18 Hz), 1.61 (t, 2 H, J = 7.5 Hz), 1.42 – 1.27 (m, 7 H), 0.89 (t, 3 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 143.7, 137.2, 128.4, 128.1, 112.3, 53.6, 26.7, 23.2, 23.1, 14.0; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1284.

3,4-Dimethyl-3-phenylthio-1-hexene (82b).

A 1.4 M hexane solution of *sec*-butyllithium (4.7 mL, 6.6 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 1-methyl-1-phenylthio-3-chloropropene **42** (1.00 g, 5.0 mmol) in 5 mL of THF. The reaction mixture was stirred for 1 h at -78 °C and then it was allowed to warm slowly to room temperature for 16 h. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 0.91 g (82%) of 3,4-dimethyl-3-phenylthio-1-hexene (**82b** – two diastereomers) as a colorless oil. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.44 – 7.24 (m, 5 H), 5.86 (dd, 1 H, J_1 = 18.0 Hz, J_2 = 9.0 Hz), 4.91 (dd, 1 H, J_1 = 9.0 Hz, J_2 = 6.0 Hz), 4.57 (dd, 1 H,

J_1 = 18.0 Hz, J_2 = 1.5 Hz), 1.54 – 1.47 (m, 1 H), 1.17 – 0.87 (m, 11 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 143.2, 142.9, 137.6, 128.4, 128.1, 112.6, 111.9, 58.9, 58.8, 43.4, 43.0, 25.3, 24.4, 18.8, 18.3, 14.7, 14.0, 12.9, 12.8; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1279.

Preparation of (*E*)-5,5-dimethyl-1-phenylthio-2-hexene (82c) in general conditions (A).

A 1.7 M hexane solution of *sec*-butyllithium (3.9 mL, 6.6 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.6 mmol) were mixed in THF (20 mL) in an argon atmosphere at -78 °C. The solution was stirred for 40 min at this temperature and then CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 1-methyl-1-phenylthio-3-chloropropene **42** (1.00 g, 5.0 mmol) in 5 mL of THF. The reaction mixture was stirred for 1 h at -78 °C and then it was allowed to warm slowly to room temperature for 16 h. The reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and the product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 1.0 g (91% yield) of *E*-5,5-dimethyl-1-phenylthio-2-hexene (**82c**) as a colorless oil. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.32 – 7.15 (m, 5 H), 5.96 (t, 1 H, J = 7.9 Hz), 2.00 (d, 2 H, J = 7.9 Hz), 1.86 (s, 3 H), 0.92 (s, 9 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 135.5, 133.4, 130.1, 128.8, 126.2, 43.2, 31.8, 29.3, 18.1; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1285.

Preparation of (*E*)-5,5-dimethyl-1-phenylthio-2-hexene (82c) in general conditions (C).

A 1.7 M hexane solution of *sec*-butyllithium (3.9 mL, 6.6 mmol) and a 0.5 M THF solution of $ZnCl_2$ (13.0 mL, 6.5 mmol) were mixed in THF (20 mL) in an argon atmosphere at -

78 °C. After being stirred for 40 min at this temperature, the reaction mixture was heated quickly to the ambient temperature and then cooled to 0 °C. CuBr•SMe_2 (~5 mol%, 0.07 g) was added in one portion followed by dropwise addition of a solution of 1-methyl-1-phenylthio-3-chloropropene **42** (1.00 g, 5.0 mmol) in 5 mL of THF. The reaction mixture was stirred for 16 h at 0 °C and then the reaction was quenched with saturated aqueous K_2CO_3 (100 mL) and the product was extracted with diethyl ether. The extract was washed with brine and then dried over $MgSO_4$. The organic solvents were removed under reduced pressure. The residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 1.0 g (91% yield) of *E*-5,5-dimethyl-1-phenylthio-2-hexene (**82c**) as a colorless oil. ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) spectra are given above.

(*E*)-5-(3-(phenylthio)allyl)-2,3-dihydrofuran (85).

2,3-Dihydrofuran (1.3 mL, 16.2 mmol) and a 1.7 M pentane solution of *t*-butyllithium (9.5 mL, 16.2 mmol) were mixed in 5 mL of THF at -78 °C and after 10 min the reaction mixture was placed in a 0 °C ice-bath for 45 min. After that the mixture was cooled to -78 °C, a 0.5 M THF solution of $ZnCl_2$ (16.2 mL, 8.1 mmol) was added dropwise. The reaction mixture was stirred for 1 h at that temperature and then CuBr•SMe_2 (~5 mol%, 0.1 g) was added in one portion followed by 1-phenylthio-3-chloropropene **36** (1.00 g, 5.4 mmol). The reaction mixture was allowed to warm slowly to room temperature and the reaction was quenched with saturated aq. K_2CO_3. The reaction was processed as usual. The crude material was passed through a short silica gel column and the product was eluted with 5% EtOAc in hexane to afford 1.00 g (86% yield) of the titled product. ^{1}H NMR (C_6D_6), δ (ppm): 7.28 – 7.00 (m, 5 H), 6.18 (d, 1 H, J = 14.8 Hz), 5.95 (m, 1 H), 4.50 (broad, 1 H), 4.10 (t, 2 H, J = 8.3 Hz), 2.83 (d, 2 H, J = 6.8 Hz),

2.35 (dt, 2 H, J_1 = 8.3 Hz, J_2 = 2.0 Hz); ^{13}C NMR (C_6D_6), δ (ppm): 158.2, 138.0, 132.3, 130.6 (2C), 128.0, 126.0, 96.4, 69.9, 33.4, 31.5.

5-Cinnamyl-2,3-dihydrofuran (87).

The procedure was the same as for **86** except that cinnamyl chloride **4** (1.0 mL, 7.2 mmol) was used instead of 1-phenylthio-3-chloropropene **36**. The crude material was passed through a short silica gel column and the product was eluted with 5% EtOAc in hexane. After removal of the solvent, the titled product was obtained as a bright yellow oil (1.30 g, 92% yield). ^{1}H NMR (C_6D_6), δ (ppm): 7.26 – 7.07 (m, 5 H), 6.37 (d, 1 H, J = 15.8 Hz), 6.20 (m, 1 H), 4.55 (broad, 1 H), 4.15 (t, 2 H, J = 8.4 Hz), 2.95 (m, 2 H), 2.38 (dt, 2 H, J_1 = 8.4 Hz, J_2 = 2.1 Hz); ^{13}C NMR (C_6D_6), δ (ppm): 157.6, 137.7, 132.3, 128.7, 127.3, 126.4, 125.5, 94.5, 69.9, 32.0, 30.3; exact mass calcd. for $C_{13}H_{14}$ 186.1045, found 186.1036.

2.0 PREPARATION OF VARIOUS ALKYLLITHIUMS BY REDUCTIVE LITHIATION OF THE CORRESPONDING ALKYL PHENYL SULFIDES WITH LITHIUM 1-(*N*,*N*-DIMETHYLAMINO)NAPHTHALENIDE

2.1 INTRODUCTION

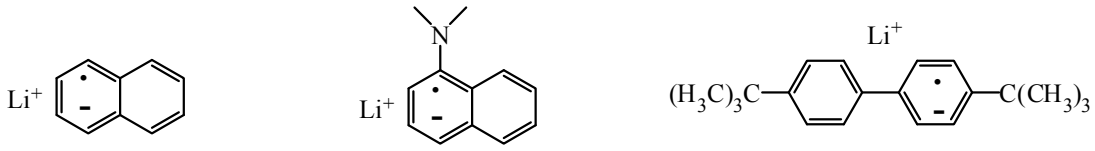
2.1.1 Lithium Radical-Anion Reagents

The transmetallation reaction of organolithiums[12] with zinc halides has proven to be one of the most synthetically useful methods for the preparation of organozinc reagents. Unfunctionalized and many functionalized organolithiums can be easily prepared by reductive lithiation or halogen-lithium exchange, while their transmetallation allows an easy and very productive access to organozinc reagents that cannot be prepared by oxidative zincation.

Aromatic radical anions are formed as a result of the abstraction of an electron from an alkali metal, usually Li, by an aromatic hydrocarbon.[61] The electron donated by the metal is believed to occupy the π^* orbital (LUMO) of the corresponding aromatic compound.[61]

Several different aromatic radical anions, such as lithium naphthalenide (LN), lithium l-(dimethylamino)-naphthalenide (LDMAN) and lithium 4,4'-di-*t*-butylbiphenylide (LDBB) are

currently in use (Scheme 2.1), as elaborated below.

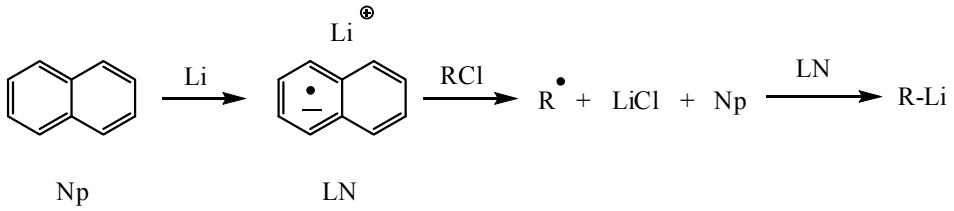


Lithium naphthalenide (LN) | Lithium 1-(dimethylamino)naphthalenide (LDMAN) | Lithium *p*,*p*'-di-*t*-butylbiphenylide (LDBB)

Scheme 2.1. Aromatic radical anion reducing agents.

The aromatic compounds naphthalene (Np), 4,4′-di-*t*-butylbiphenyl (DBB) and 1-(dimethylamino)-naphthalene (DMAN) also may serve simply as a "storehouse" for one or two electrons in the absence of an H^+-donor. In the presence of a receptor, an electron is transferred to it, and then the receptor undergoes a variety of product-forming transformations depending on its nature.

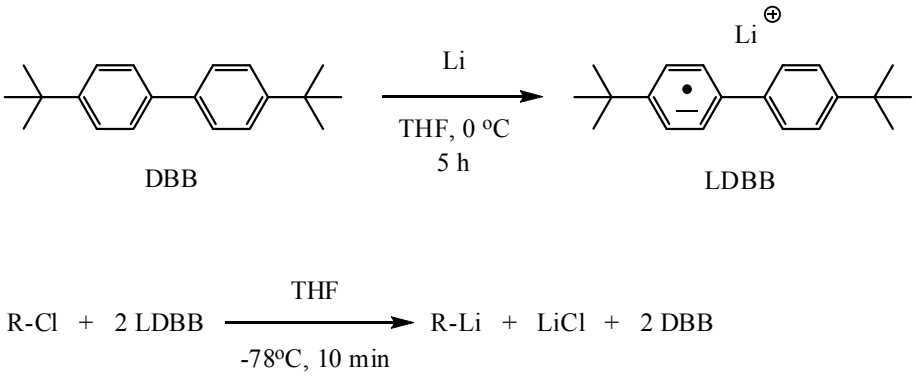
The formation of aromatic radical anions is dependent on the nature of metal, the hydrocarbon, the temperature, and the solvent. Screttas,[62] in 1972, was the first to report aromatic radical anions formed from lithium and naphthalene. The latter acts as an acceptor of lithium's electron, and the resulting radical anion LN (Scheme 2.2) is used for a very rapid reduction of an alkyl halide to generate an alkyl radical, which then accepts another electron from next LN molecule in order to form an alkyllithium (RLi).[62] Alkylsodiums (RNa) and alkylpotassiums (RK) also have been generated by this reductive metallation reaction,[63] but they are far more basic than alkyllithiums and are immediately protonated by solvent or starting material to give RH, plus a considerable amount of naphthalene-derived by-product.[62]



Scheme 2.2. Formation of LN and its use in reductive lithiation of an allyl chloride.

There were still problems with the use of LN, mainly arising from the susceptibility of naphthalene or its radical-anion to attack by the intermediate radical ($R^{\bullet}$) or by the newly formed organolithium (RLi). To solve this problem, another aromatic radical-anion LDBB was developed by Freeman[64] for use in place of the less reliable LN.

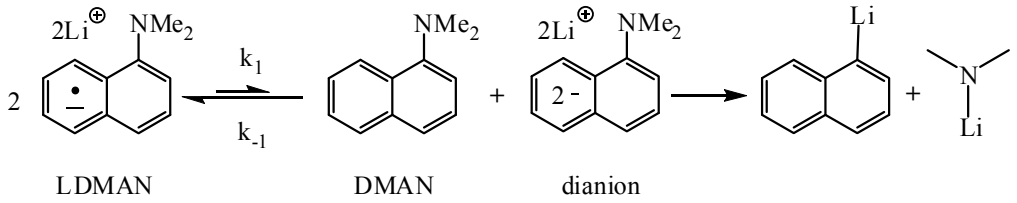
The lithium radical-anion reagent LDBB is formed from Li metal and the aromatic hydrocarbon DBB and possesses bulky *t*-butyl groups that effectively prevent its participation in side-reactions by shielding all positions in both aromatic rings while allowing it to participate in single electron reductions. LDBB is also a more powerful electron donor than LN and allows reductive lithiation to be performed at a much lower temperature and in a shorter time. For instance, LDBB in THF solutions at –78 °C promotes the formation of carboxylic acids, derived from reductive lithiation of alkylchlorides followed by addition of CO_2, in higher than 90% yields.[62] The reductive lithiation is fast even at –100 °C, diminishing even further potential problems due to side-reactions.



Scheme 2.3. Formation of LDBB and its use in reductive lithiation.

Unfortunately, the use of LDBB for the preparation of various alkyllithiums in large scale processes is strictly limited by the separation problem which lowers yields considerably or makes the whole separation process practically impossible. When the actual reaction is finished the aromatic hydrocarbon by-product DBB can be removed either by using a long chromatography column, if the desired product is fairly polar, or by vacuum distillation, which is usually too destructive and results in low isolated yields.

In 1980, a solution to the problem of removal of the aromatic hydrocarbon was found in the Cohen laboratory.[65] When lithium 1-(dimethylamino)-naphthalenide (LDMAN, Scheme 2.1) was used as the reducing agent, the basic aromatic by-product DMAN could be easily removed and recovered by a dilute acid wash and of course it could be recycled. An additional advantage of the use of LDMAN is that it can be used in solvents other than THF, the solvent universally used in synthetic procedures involving aromatic lithium radical-anions.[66] A disadvantage of LDMAN is that above -45 °C it decomposes to 1-lithionaphthalene and lithium dimethylamide; it has been speculated[65] that this decomposition proceeds through a minor amount of aromatic dianion in equilibrium with LDMAN (Scheme 2.4).



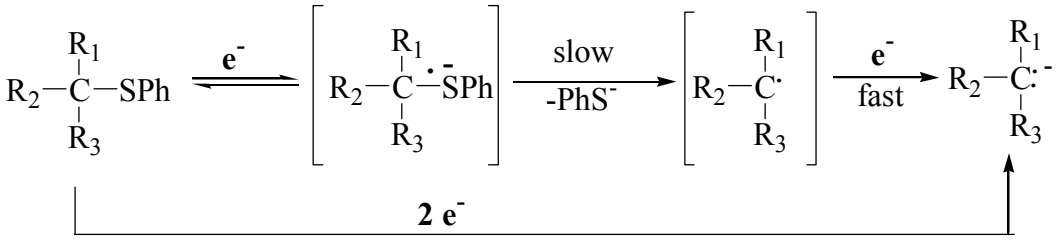
Scheme 2.4. When the temperature is higher than -45 °C, LDMAN decomposes, probably through a minor amount of aromatic dianion in equilibrium with LDMAN.

This often appeared to be only a minor disadvantage since most reductive lithiations are successful at -78 °C. The use of LDMAN is rather widespread,[65,66, 67,68,69] but considerably less so than the use of LDBB.[70,71] The reason for the preference for LDBB is that, except in cases in which there is a separation problem, LDBB generally gave reproducible results and somewhat superior yields than LDMAN.[72,67a] It is noteworthy that the limitation of using THF as solvent, when the newly formed organolithium self-destructs by removing a proton from THF at temperature higher than 0 ˚C, has been recently overcome by using LDMAN in dimethyl ether to generate the radical anion.[66]

2.1.2 Reductive Lithiation of Alkyl Phenyl Sulfides

Since its introduction in 1978,[73,74] reductive lithiation of phenyl thioethers using aromatic radical-anions has been demonstrated to be one of the most versatile methods known for generating organolithiums.[75,76] A number of other leaving groups, such as halides,[77] sulfones,[78] sulfates,[79] nitriles,[80] selenides,[81] allylic and benzylic ethers,[82] amines,[83] and acetals,[84] have also been used but they have been considerably less versatile than the phenylthio group.[85]

An important advantage of reductive lithiation is that unlike the most conventional method of organolithium preparation, removal of an electrophile such as H^+, I^+, R_3Sn^+, etc. by another organolithium, it is often the case that the less stable the organolithium, the greater the ease of its generation by reductive lithiation. The reason, as shown in Scheme 2.5 for phenylthioethers, is that the mechanism[86] of reductive lithiation involves the reversible transfer of an electron from the reducing aromatic radical-anion agent to the substrate followed by a homolytic cleavage of the bond between the organic moiety and the leaving group.[87] Since this step is rate determining, the rate of the reaction is determined largely by the stability of the intermediate radical, rather than that of the carbanion to which the radical is rapidly reduced by the second equivalent of radical-anion reagent. Thus, less stable carbanions are often produced more readily (tertiary anions > secondary anions > primary anions and $sp^3 > sp^2$) due to the opposite stability order of carbanions and the corresponding carbon radicals. Therefore, it is an extremely general method of organolithium production, especially since phenyl thioethers are available by a wide variety of synthetic methods, many of them connective.

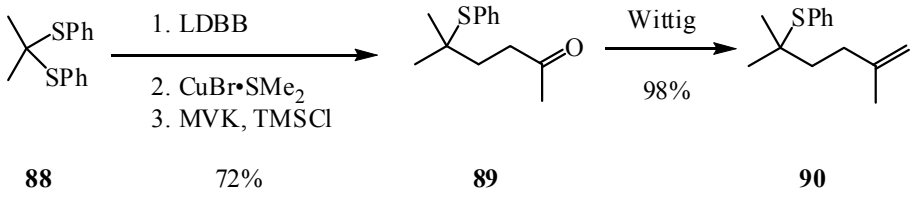


Scheme 2.5. Mechanism of reductive lithiation.

Another considerable advantage is that the aromatic and the thiophenol are recoverable and thus a stoichiometric amount of lithium metal is the only reagent that is destroyed, making

this the most economical method available since lithium is far less expensive than any organic form of lithium.

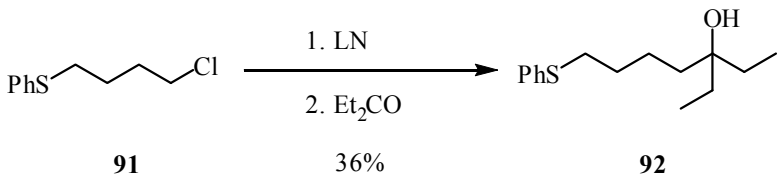
Numerous examples of reductive lithiation of alkyl sulfides by LDBB, LN and LDMAN have been reported. For instance, reductive lithiation of 2,2-bis(phenylthio)propane **88** with LDBB followed by capturing the product with methyl vinyl ketone (MVK) in the presence of cuprous bromide and TMSCl led to formation of the corresponding ketone **89,** which can be separated from the aromatic byproduct DBB by using column chromatography (5% EtOAc/hexane, R_f = 0.1) or vacuum distillation.[88] Both purification methods led to moderate isolated yields of **89**. Subsequent, nearly quantitative, Wittig olefination afforded the 2,5-dimethyl-5-phenylthiohexene **90** in 70% yield over two steps (Fig 2.6).



Scheme 2.6. Using reductive lithiation of 2,2-bis(phenylthio)propane **88** with LDBB in the synthesis of 2,5-dimethyl-5-phenylthiohexene **89**.

Recently, Yus and co-workers reported results observed on selective reductive lithiation of certain 1-chloro-n-phenylsulfanylalkanes (where "n" is a position of the phenylsulfanyl substituent in a molecule) with LN capturing the organolithium with diethyl ketone.[89] Although the C-Cl group was successfully reduced by LN in the presence of the SPh-functionality in substrates such as **91** (Scheme 2.7), the isolated yields observed were only moderate, presumably due to a very slow column chromatography on silica gel (10% EtOAc/hexane; R_f = 0.11)

required for effective separation (Scheme 2.7).[89] It is also possible that a slow chromatography over silica gel could affect the tertiary alcohol **92** by catalyzing the elimination reaction.



91 36% **92**

Scheme 2.7. Selective reductive lithiation of certain 1-chloro-4-phenylsulfanybutane with LN.

There are many other considerably successful examples of using reductive lithiation of alkylsulfides by LDBB or LN. Unfortunately, most of them, as in the examples given in Schemes 2.5 and 2.6, suffer from the same disadvantage, which consists of diminished isolated yields due to purification problems associated with the aromatic by-product DBB or LN.

More recently, Yus and co-workers introduced the use of the catalytic aromatic method as another way to solve the problem of separation of the desired products from aromatic hydrocarbon by-products. In their extensive work,[90,91, 92] a solution of the substrate to be reduced in THF is mixed with from 1 to 5 mole % of the aromatic, usually naphthalene or 4,4'-di-*tert*-butylbiphenyl (DBB), and a large excess of specially prepared lithium powder, usually a 4 to 7 fold molar excess. It was demonstrated that a large variety of organic compounds can be reductively lithiated in the presence of only a catalytic amount of an aromatic hydrocarbon auxiliary, and that this method simplifies the separation of the reaction product from the aromatic.[90-92]

In a number of these papers, it is claimed that the catalytic aromatic method (CA), in which the radical-anion is continually generated and rapidly destroyed by electron transfer to the

substrate, is far more powerful than the use of a stoichiometric amount of preformed aromatic radical-anion (PAR).[92, 93, 94, 95, 96]

This claim, however, seemed unlikely to us based on the experimental results enumerated above and some other results from our laboratory.[97] The theoretical basis also appears inconsistent with our experience that radical-anion formation is always slower than the reductive lithiation. Thus, in most cases the rate-determining step in the CA reductive lithiation would be the transfer of an electron from the surface of the metal to the aromatic catalyst. The net result would be that the process of reductive lithiation would be slower at any given temperature than the process using preformed radical anion as in PAR method. Such longer reaction times can in some cases translate into destruction of some organolithium compounds. This makes Yus's CA method at least "not general"; for instance this method can never be recommended for the preparation of tertiary alkyllithiums. Of course, damage is minimized in the Yus protocol in which the radical-anion formation is accelerated by supplying the lithium as a freshly prepared fine powder instead of larger chunks with less surface area and by the use of a very large excess of lithium. This dramatically increases the overall price and complexity of Yus's CA method, while the regular PAR reductive lithiation can be performed in any laboratory without the use of special equipment necessary to prepare and operate with fine lithium powder. Moreover, the rate-determining step is still the electron transfer to the aromatic catalyst as evidenced by the fact that, as in the use of the catalytic method with LDMAN mentioned above,[98] the color of the radical-anion does not appear until all of the reduction substrate has been consumed.[93, 99]

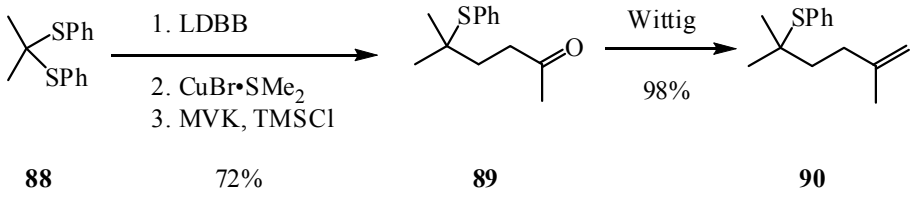
2.2 RESULTS AND DISCUSSION

2.2.1 LDMAN Preparation Procedure

A careful reexamination of the general procedure[100] for the preparation of LDMAN has now revealed a previously unrecognized problem, the elimination of which makes LDMAN the reagent of choice in reductive lithiations. The problem is that the decomposition of LDMAN in THF actually commences at a noticeable rate even below -45 °C, while at temperatures below -60 °C the single electron transfer process involved in aromatic radical-anion formation becomes extremely slow. Unfortunately, most commonly used laboratory temperature controllers do not maintain a very constant temperature. For optimum yield, it is necessary to not allow the temperature to rise above -52 °C. We have found that this is best accomplished by maintaining a temperature of -55±3 °C by manual control. Under these conditions, the preparation takes about 5.5 hours. At a lower temperature, the time that the control must be maintained becomes impractical. Moreover, it is important to use lithium ribbon free of oxide film, which can be easily removed by scraping in dry light mineral oil. When LDMAN is prepared according to the protocol described above and the general procedure for reductive lithiation with LDMAN, as described below, is followed, every example that we have tested provides higher yields than the use of LDBB.

Reductive lithiation of 2,2-bis(phenylthio)propane **88** with LDMAN followed by capturing the product with methyl vinyl ketone (MVK) in the presence of TMSCl and cuprous bromide led to formation of the corresponding ketone **89** and basic aromatic amine DMAN (Scheme 2.8), which was completely washed out with dilute aqueous HCl. Therefore, the use of LDMAN instead of LDBB[88] provided the essentially pure ketone **89** in 95% yield. This result

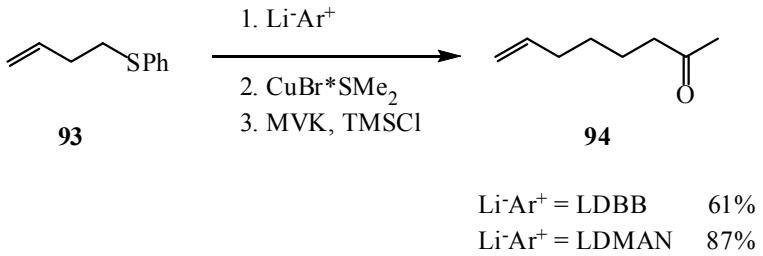
should be compared to the 72% yield of **89** produced when LDBB was used as the reductive lithiation reagent (Scheme 2.6).[88] The ketone **89**, produced by the reductive lithiation with LDMAN, was immediately submitted to Wittig olefination without the need of any further purification. Thus, the desired 2,5-dimethyl-5-phenylthiohexene **90** was produced in 93% overall isolated yield (Scheme 2.8).



88 72% **89** **90**

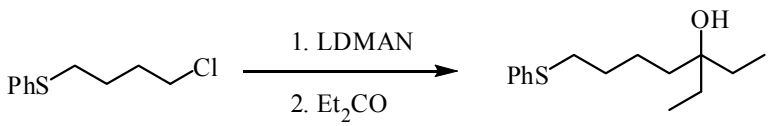
Scheme 2.8. The use of reductive lithiation of 2,2-bis(phenylthio)propane **88** with LDMAN in the synthesis of 2,5-dimethyl-5-phenylthiohexene **89**.

When the synthesis of 7-octen-2-one **94** was performed on a preparative scale using reductive lithiation of starting 4-phenylthio-1-butene **93** with LDBB, the subsequent column separation of the product **94** from a large amount of aromatic by-product DBB is inconvenient. Vacuum distillation performed instead afforded the pure product **94** with only a moderate yield (Scheme 2.9). On the other hand, when LDBB was replaced with LDMAN, properly prepared, the aromatic basic by-product DMAN was removed with a dilute acid wash and then fast column chromatography was successfully performed in order to afford the pure product **94** with 87% yield (Scheme 2.9).



Scheme 2.9. Large scale preparation of 7-octen-2-one **94** using reductive lithiation of the starting 4-thiopenyl-1-butene **93** with either LDBB or LDMAN.

In order to demonstrate its considerable potential as a reliable reagent for reductive lithiation, LDMAN was utilized in selective lithiation of 1-chloro-4-thiophenylbutane **91** (Scheme 2.10) and the results were compared with the 36% yield reported by Yus and co-workers for use of LN (Scheme 2.7).[89] Because aromatic by-product DMAN was found to react extremely fast with 3 M aqueous HCl, it was possible to use only a stoichiometric amount of this acid in order to wash out DMAN completely and these conditions caused no harm to the tertiary alcohol product **92**. Such chemically activated extraction-purification allowed us to obtained essentially pure product, which was further purified by fast column chromatography using either basic alumina (93% yield) or even regular silica gel (82% yield) of the purified product **92** (Scheme 2.10). It is noteworthy that after being exposed to slow silica gel column chromatography, the yield of the desired alcohol **92** diminished dramatically to a moderate 65% (Scheme 2.10), presumably due to an elimination reaction catalyzed by acidic sites of the regular silica gel. This observation could explain the low yields observed by Yus,[89] when extremely slow silica gel column was used for purification to get rid of aromatic hydrocarbon by-product LN (Fig 2.7).



91 **92**

93% (basic Al_2O_3 - column)
82% (regular SiO_2 - fast column, $R_f = 0.6$)
65% (regular SiO_2 - slow column, $R_f = 0.2$)

Scheme 2.10. Selective reductive lithiation of 1-chloro-4-phenylthiobutane with LDMAN.

2.2.2 Conclusions

LDMAN should be recognized as a reductive reagent which is far superior to LDBB and LN due to the wide range of benefits offered by this reagent, provided that proper temperature control is maintained during its generation. LDMAN is a powerful reducing agent chemically stable against even tertiary alkyllithiums formed during reductive lithiations at -78 °C. Due to its fairly high Lewis basicity, DMAN can be easily and completely washed out during the work-up process with dilute aqueous HCl, even in the case of acid-sensitive products. Being a weaker reducing agent than LDBB, LDMAN can be effectively used in certain selective reductive lithiations.

2.3 EXPERIMENTAL SECTION

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C at 22°C. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of the $CDCl_3$ triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). Coupling constants, J, are reported in Hz. High resolution mass spectra were recorded on a CH-5 double focusing Varian MAT or on VG 70-SE mass spectrometer.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled over sodium metal in the presence of benzophenone as indicator. Hexane was distilled over CaH_2.

General Experimental Procedures. All reactions were carried out under a positive pressure of dry argon gas in oven-dried (140 °C) flasks and standard precautions against moisture were taken. Flash column chromatography (low pressure) was performed either with Silicycle Silia-P Flash silica gel (40-63 μm, surface area – 500 m^2/g) or with Sigma-Aldrich basic aluminum oxide (150 mesh, 58 Å, activated). Thin-layer chromatography was performed on glass supported 250 μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one of the following: 254 nm UV light and aqueous solution of $KMnO_4$ (1%) with NaOH (1%) and K_2CO_3 (6%). A dry ice/acetone bath was used to obtain temperatures of –78 °C. An ice bath was used to obtain 0 °C. An acetone bath equipped with a cryogenic cooler Flexi-Cool

FC-100 was used to obtain -84 °C and -55 ± 3 °C (the observed difference between the in-bath and the in-flask temperatures has never been greater than 1 °C for a 250 mL round bottom flask used in all radical-anion experiments). Anhydrous magnesium sulfate was used as the drying reagent.

Representative procedure for LDMAN preparation.

To a three-neck round bottom flask, equipped with a magnetic stirrer, argon inlet and a rubber septum was added 40 mL of dry THF. The flask was cooled to -55 °C (external cooling bath temperature). Lithium ribbon was prepared by scraping the dark oxide coating off of the surface with a scalpel, while a piece of lithium ribbon was immersed in fresh mineral oil. The shiny metal was dipped in to dry hexane in order to remove the oil and then weighed (0.185 g, 26.8 mmol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexane prior to addition to the flask. Then DMAN (4.9 mL, 30.0 mmol) was added quickly via syringe at -55 °C (external cooling bath temperature). A green color appeared in less than two minutes and became deep green in less than 5 minutes. The reaction mixture was stirred for 5 h at -55 ± 3 °C (external cooling bath temperature). The LDMAN thus prepared was suitable for reductive lithiation on a 12.7 mmol scale.

Representative procedure for LDBB preparation.

To a flame-dried three-neck round-bottom flask, equipped with a glass-coated stirring bar, argon inlet and rubber septum was added 4,4'-di-*tert*-butylbiphenyl (DBB) (8.00 g, 30.0 mmol). Lithium ribbon was prepared by scraping the dark oxide coating off of the surface with a

scalpel, while a piece of lithium ribbon was immersed in mineral oil. The shiny metal was dipped in hexanes in order to remove the oil and then weighed (208 mg, 30.0 mmol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexane prior to addition to the flask. THF (80 mL) was added to the DBB/lithium mixture via syringe. The reaction mixture was stirred at room temperature for about 5 min until a dark-blue color appeared on the lithium surface and it was then allowed to cool to 0 °C and stirred for 5 h. The resulting dark-blue solution of LDBB was ready for use in reductive lithiation (~14.0 mmol scale).

2,2-Bis(phenylthio)propane (88).[101]

A 250 mL one neck round bottom flask equipped with a rubber septum was purged three times with argon gas and charged with a solution of 3.0 mL (50 mmol) of acetone and 10.3 mL (100 mmol) of thiophenol in 50 mL of dry dichloromethane. TMSCl (9.5 mL, 75 mmol) was added dropwise over a period of 30 min at room temperature. The resulting mixture was stirred for about 16 h at ambient temperature. The reaction was quenched with 100 mL of a 1M aqueous solution of NaOH. The product was extracted with dichloromethane and then washed with brine. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over basic alumina (5% EtOAc/hexane) to afford 9.4 g (73%) of the titled product. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.65 – 7.62 (m, 4 H), 7.30 – 7.23 (m, 6 H), 1.48 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 136.7, 132.1, 128.8, 128.3, 59.2, 30.6.

5-Methyl-5-phenylthio-2-hexanone (89).

A solution of LDMAN (73.0 mmol), freshly prepared in THF (100 mL) at -55 °C, was cooled to -78 °C and treated with 2,2-bis(phenylthio)propane **88** (9.00 g, 34.8 mmol) in dry THF (10 mL). After the solution had been stirred for 30 min at -78 °C, copper bromide-dimethyl sulfide complex (7.87 g, 38.2 mmol) was quickly added under increased argon flow. The cuprate formation was ensured by stirring the reaction mixture at -78 °C for 2.5 h. The reaction mixture was cooled to -82 °C and then trimethylsilyl chloride (6.6 mL, 52.0 mmol) and methyl vinyl ketone (3.4 mL, 42.0 mmol), premixed in 10 mL dry THF, were added slowly by syringe pump in order to maintain the reaction mixture temperature below -78 °C. The mixture was stirred at -78 °C overnight. The reaction mixture was allowed to warm slowly to -10 °C and aqueous 1M NaOH solution (150 mL) and about 1 mL of tetrabutylammonium hydroxide were added. It was stirred at room temperature for 1 h in order to hydrolyze all of the silyl enol ether to the ketone product and then was poured into diethyl ether (300 mL) to precipitate all of CuSPh. After the mixture had been filtered, the layers were separated and the organic material was extracted with diethyl ether (2 × 100 mL). The organic layers were combined and stirred with 240 mL of 3M aqueous HCl to remove DMAN completely. The layers were separated and the organic product was extracted by ether (2 × 100 mL). The combined organic layers were washed with saturated aqueous K_2CO_3 and then dried over $MgSO_4$. The organic solvents were removed by rotary evaporation to afford 7.26 g (95% yield) of the essentially pure titled product **89** as an orange oil, which was used in next step without further purification. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.49 – 7.30 (m, 5 H), 2.70 (t, 2 H, J = 7.6 Hz), 2.16 (s, 3 H), 1.72 (t, 2 H, J = 7.6 Hz), 1.21 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 208.1, 137.2, 131.6, 128.6, 128.4, 48.4, 39.3, 34.9, 29.9, 28. These NMR data agreed well with the literature values.[88]

2,5-Dimethyl-5-phenylthio-1-hexene (90).

To a suspension of methyl triphenylphosphonium bromide (7.32 g, 20.5 mmol) in THF (70 mL) at 0 °C, a 1.6 M hexane solution of *n*-butyllithium (11.8 mL, 18.9 mmol) was added dropwise. The mixture was stirred at 0 °C for 15 min; it was then cooled to -78 °C and a solution of 5-methyl-5-phenylthio-2-hexanone (**89**) (2.50 g, 11.4 mmol) in THF (10 mL) was added dropwise. After being stirred at -78 °C for 15 min, the reaction mixture was warmed to 0 °C, stirred for 30 min, and the reaction was quenched with 1 mL of methanol. The mixture was poured into 250 mL of pentane and filtered through silica gel. The solvent was removed by rotary evaporation. Flash chromatography (5% EtOAc/hex) provided the titled product as a colorless oil 2.43 g (98% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.52 – 7.25 (m, 5 H), 4.63 (s, 2 H), 2.24 – 2.19 (m, 2 H), 1.73 (s, 3 H), 1.62 – 1.56 (m, 2 H), 1.24 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 145.7, 137.4, 132.2, 128.6, 128.3, 109.6, 48.9, 40.2, 32.9, 28.7, 22.7; exact mass calcd. for $C_{14}H_{20}S$ 220.1286, found 220.1280. These NMR data agreed well with the literature values.[88]

Preparation of 1-chloro-4-phenylthiobutane (91).[89]

Thiophenol (16.0 mL, 0.153 mol) was added to a solution of KOH (9.2 g, 0.164 mol) in 300 mL of MeOH at room temperature. After 30 min, 25.0 g (0.146 mol) of 1-bromo-4-chlorobutane was added and stirring was continued at ambient temperature for 24 h. Then the solvent was removed in a rotary evaporator. Water (200 mL) was added and the organic product was extracted with dichloromethane. The extract was washed with 200 mL of a 1 M aqueous solution of NaOH and then with brine. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (5% EtOAc/hexane) to afford

20.5 g of the titled product **91**. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.33 – 7.13 (m, 5 H), 3.50 (t, 2 H, *J* = 6.6 Hz), 2.91 (t, 2 H, *J* = 6.6 Hz), 1.91 – 1.72 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 136.2, 129.1, 128.8, 125.8, 44.3, 32.8, 31.3, 26.2.

Preparation of 7-Phenylthio-3-ethylheptan-3-ol (92) by reductive lithiation of 91 with LDMAN.

A solution of LDMAN (17.3 mmol) prepared at -55 °C in THF (40 mL) was cooled to –88 °C and a solution of **91** (1.65 g, 8.25 mmol) in THF (5 mL) was added quickly. The reaction mixture was warmed to -78 °C in 10 min and stirred at this temperature for 20 min. A solution of diethylketone (1.0 mL, 10.0 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to ambient temperature overnight and quenched with 100 mL of brine solution. The layers were separated and the product was extracted with diethyl ether (3 × 50 mL). The combined organic layer was shaked with 8 mL of 3M HCl (~20 mmol) and then washed with saturated aqueous K_2CO_3. The extract was dried over $MgSO_4$ and the organic solvents were removed by rotary evaporation. Flash chromatography on silica gel (20% EtOAc/hexanes, R_f = 0.6) gave the title product **92** as a colorless oil, 1.70 g (82% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32 – 7.13 (m, 5 H), 2.91 (t, 2 H, *J* = 6.9 Hz), 1.65 – 1.61 (broad, 2 H), 1.46 – 1.37 (m, 9 H), 0.83 (t, 6 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ(ppm): 136.6, 128.7, 128.6, 125.5, 74.2, 37.5, 33.3, 30.7, 29.5, 22.4, 7.6; exact mass calcd. for $C_{15}H_{24}OS$ 252.1548, found 252.1550. These NMR data agreed well with the literature values.[89]

4-Phenylthio-1-butene (93)

A 250 mL three-neck round-bottom flask equipped with condenser, addition funnel and glass stopper was charged with 75 mL of water and 2.8 g (70 mmol) of NaOH. Thiophenol (7.5 mL, 70 mmol) was added to the solution dropwise. The reaction mixture was stirred for 30 min to insure the complete formation of sodium thiophenoxide. 4-Bromo-1-butene (10.0 g, 74 mmol) in 15 mL of ethanol was added slowly at room temperature. The resulting reaction mixture was stirred at the same temperature for 24 h. The product was extracted with dichloromethane. The organic extract was washed with 100 mL of a 1 M aqueous solution of NaOH and then with brine. The extract was dried over magnesium sulfate and the organic solvents were rotary evaporated to afford 11.3 g (98% yield) of crude but essentially pure 4-phenylthio-1-butene (**93**). ^{1}H NMR ($CDCl_3$)[14] δ (ppm): 7.33 – 7.14 (m, 5 H), 5.87 – 5.76 (m, 1 H), 5.10 – 5.01 (m, 2 H), 2.95 (t, 2 H, J = 7.2 Hz), 2.36 (q, 2 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 136.3, 136.2, 129.0, 128.7, 125.8, 116.1, 33.2, 32.8.

Preparation of 7-octen-2-one (94) by the reductive lithiation of 93 with LDMAN.

A solution of LDMAN (35.5 mmol), freshly prepared in THF (50 mL) at -55 °C, was cooled to -78 °C and treated with 4-phenylthio-1-butene **93** (2.77 g, 16.9 mmol) in dry THF (10 mL). After the solution had been stirred for 1 h at -78 °C, copper bromide-dimethyl sulfide complex (3.50 g, 17.0 mmol) was quickly added under increased argon flow. The cuprate formation was ensured by stirring the reaction mixture at -78 °C for 2.5 h. The reaction mixture was cooled to -82 °C and then trimethylsilyl chloride (3.2 mL, 25.0 mmol) and methyl vinyl ketone (1.8 mL, 22.0 mmol), premixed in 10 mL of dry THF, were added slowly by syringe pump to maintain the reaction mixture temperature below -78 °C. The mixture was stirred at -78

°C overnight. The reaction mixture was allowed to warm slowly to -10 °C and aqueous 1M NaOH solution (100 mL) and about 1 mL of tetrabutylammonium hydroxide were added. It was stirred at room temperature for 1 h in order to hydrolyze all of the silyl enol ether to the ketone product and then was poured into diethyl ether (200 mL) to precipitate all of the CuSPh. After the mixture had been filtered, the layers were separated and the organic materials were extracted by diethyl ether (2×50 mL). The organic layers were combined and stirred with 240 mL of 3M aqueous HCl. The layers were separated and the organic product was extracted with ether (2 × 50 mL). The extract was washed with saturated aqueous K_2CO_3 and then dried over $MgSO_4$. The solvents were removed by rotary evaporation. Flash chromatography (10% EtOAc/hexanes) gave the titled product as a yellow oil, 1.85 g (87%). ^{1}H NMR ($CDCl_3$) δ (ppm): 5.78 – 5.72 (m, 1 H), 5.01 – 4.83 (m, 2 H), 2.42 (t, 2 H, *J* = 7.0 Hz), 2.11 – 2.01 (m, 5 H), 1.62 – 1.52 (m, 2 H), 1.42 – 1.32 (m, 2 H); ^{13}C NMR ($CDCl_3$)[15] δ (ppm): 207.6, 137.7, 114.0, 42.7, 32.9, 29.0, 27.8, 22.6.

Preparation of 7-octen-2-one (94) by reductive lithiation of 93 with LDBB.

The same procedure as that for the previous LDMAN case was used except that LDBB (34.0 mmol), freshly prepared at 0 °C in 80 mL of dry THF, was used for the reductive lithiation of 4-phenylthio-1-butene (2.77 g, 16.9 mmol) at -78 °C. After rotary evaporation the desired product was distilled out at approximately 80 °C using oil-pump distillation to afford 1.3 g (61% yield) of the titled product **94**. The ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) spectra and elemental analysis of (**94**) are given above.

3.0 EFFECTIVE CONVERGENT ENANTIOSELECTIVE SYNTHESIS OF A (*R*)-DIHYDRO-α-IONONE. APPLICATION OF THE ORGANOZINC γ-ALLYLIC SUBSTITUTIONS FOR SYNTHESIS OF A POTENTIAL PRECURSOR OF THE PYRROLIZIDINE TYPE PRODUCTS

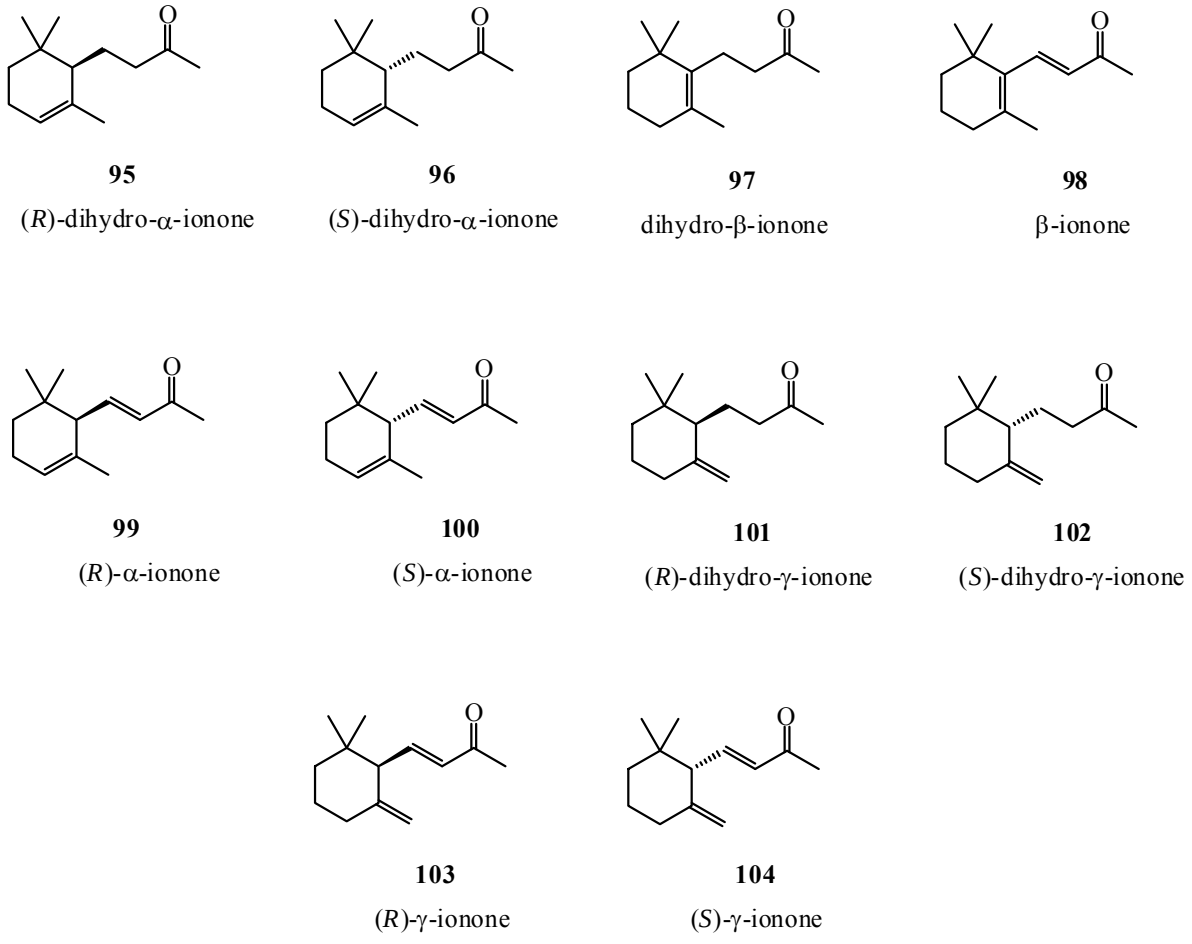
3.1 INTRODUCTION

3.1.1 Optically Active Ionones and their Derivatives: Properties and Preparation.

The stereoselective formation of new carbon–carbon bonds is an important field of research. As has been mentioned, copper (I) catalyzed allylic substitutions, which have high anti-selectivity, are especially convenient for transferring the chirality of a C–X bond to a C–C bond.[26,34,42] In Chapter 1, the remarkable ability of monoalkylzincs to undergo highly regioselective copper(I) catalyzed γ-allylic substitution has been demonstrated. The enantioselective synthesis of terpenoids, such as (R)-dihydro-α-ionone **95** (Scheme 3.1), can serve as a good demonstration of possible applications of this method along with reductive

lithiation used for the preparation of necessary alkylzinc reagents from the corresponding alkyl phenylsulfides.

In the search for the odorous principle of violets, a mixture of isomeric ionones was first prepared in 1893 by Tiemann and Krüger.[102] Indeed, even though Tiemann and Krüger did not anticipate it, α- and β-ionones (**99** and **98**, Fig 3.1) make up almost 57% of the headspace of violets in bloom.[103] Since then, ionones and dihydroionones have been established among the most highly valued fragrance constituents as a result of their distinctive fine violet and rose scents.[104,105]



Scheme 3.1. α-, β- and γ-isomers of ionones and dyhidro-ionones.

Several syntheses of natural products, such as carotenoids, edulan derivatives and theaspiranes, as well as various odoriferous substances, such as Ambrox®, made use of dihydro derivatives **95** – **97**, **101** and **102** as starting materials.[106] The synthesis of these compounds in enantiomericly pure forms requires optically active starting materials. Thus, the enantioselective preparation of these chiral building blocks (**95** – **97**, **101** and **102**) has become an important research topic, especially, in recent decades.

Two different approaches for the preparation of **99** and **100** have been reported in the literature, the resolution of the racemate[107,108] and enantioselective syntheses.[109,110]

Moreover, a potentially highly valuable use of dihydroionones would consist in their conversion to the corresponding ionones (**99, 100**, **103** and **104**), for example in two classic steps through the selective formation and elimination of an α-selenoxide as was applied by Ohigashi for the synthesis of (±)-persenone A,[111] which would make these terpenes highly valued not only as fragrances but also as substrates for the synthesis of enantiomericly pure ionones. The use of dihydroionones as substrates could dramatically simplify the preparation of enantiomericly pure ionones, which otherwise involves complicated and long processes as can be seen from several examples given below. Thus, a synthesis of an enantiomericly pure dihydro-ionone can be considered as a potential formal synthesis of the corresponding ionone.

(±)-α-Ionone was first resolved in 1943 by Sobotka and co-workers[107] using fractional crystallization of suitable diastereoisomeric derivatives. A racemic mixture of (±)-α-ionone was converted into a mixture of D- and L-α-ionone L-menthylhydrazones, which crystallized readily. Still, these were difficult to separate, because of only slight differences in their solubilities. However, the less soluble hydrazone was finally obtained in pure form after ten recrystallizations. The other diastereoisomer was obtained in modest yield and with lower

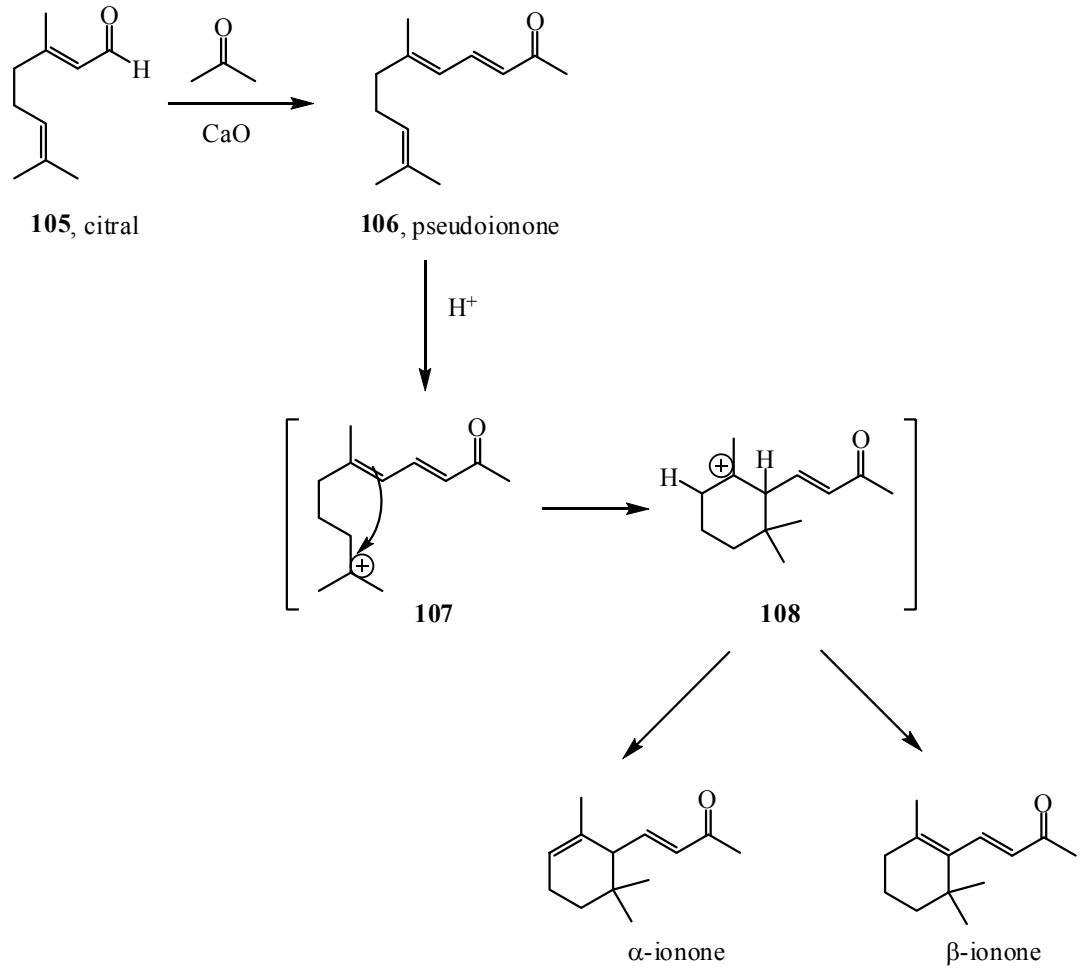
optical purity after ‘‘*twice as many recrystallizations*’’.[107] The procedure permitted the recovery of (–)-(*S*)-ionone **100** from the less soluble hydrazone, and of (+)-(*R*)-ionone **99** from the more soluble diastereoisomer, with $[\alpha]_D^{20}$ values of –406 and +347, respectively.

A few years later, in 1947, Naves[112] investigated the optical resolution of α-ionone by derivatization with menthyl aminocarbamate. It was noticed that during the hydrolysis of the crystalline diastereoisomers in the presence of phthalic acid, oxalic acid, or sulfuric acid, isomerization to β-ionone took place rather than racemization. The phenomenon was verified by UV spectroscopy, and occurred to a greater extent in the recovery of (*R*)-α-ionone. It was therefore considered to purify the obtained ionones by conversion into the corresponding semicarbazones, which should be hydrolyzable under milder conditions. The samples of (*R*)-and (*S*)-ionones obtained in this way had $[\alpha]_D^{20}$ values of +401 and –408, respectively (*c* = 4, benzene).[112] Naves also hydrogenated α-ionones to dihydro- and tetrahydroionones, and characterized them by their semicarbazone and 2,4-dinitrophenylhydrazone derivatives.

The same procedure was employed by Eugster[113] in the preparation of (*R*)- and (*S*)-α-ionones, required as precursors in the synthesis of the corresponding ε-carotene enantiomers. Recrystallizations of the L-menthyl hydrazones afforded (*R*)-ionone with $[\alpha]_D^{20}$ = +415 and (*S*)-ionone with $[[\alpha]_D^{20}$ = –403 (in EtOH). A higher optical rotation was assigned to (*R*)-ionone by Eugster in a later work.[114] To avoid losses in optical activity, he performed the hydrolysis of the (+)-hydrazone in acetic acid in the presence of pyruvic acid. Unlike Naves, he attributed this decrease in the optical rotation to racemization under more strongly acidic conditions. Once optimized, this optical resolution process was exploited for the preparation of (*R*)-and (*S*)-α-ionone, starting materials in the synthesis of various carotenoid derivatives.[114,115]

Highly enantioselective enzyme-based syntheses of useful precursors of ionones have been published recently. They are exemplified by the preparation of (*R*)-α-ionone **99** (85% ee) by Pfander[110] and of **99** (98% ee) and (*S*)-α-ionone **100** (97% ee) by Fuganti.[108,116] These achievements, though still quite laborious, compare favorably with the original preparation of α-ionone enantiomers based on a classical resolution through multiple tedious fractional crystallization of derivatives.[107,112,113]

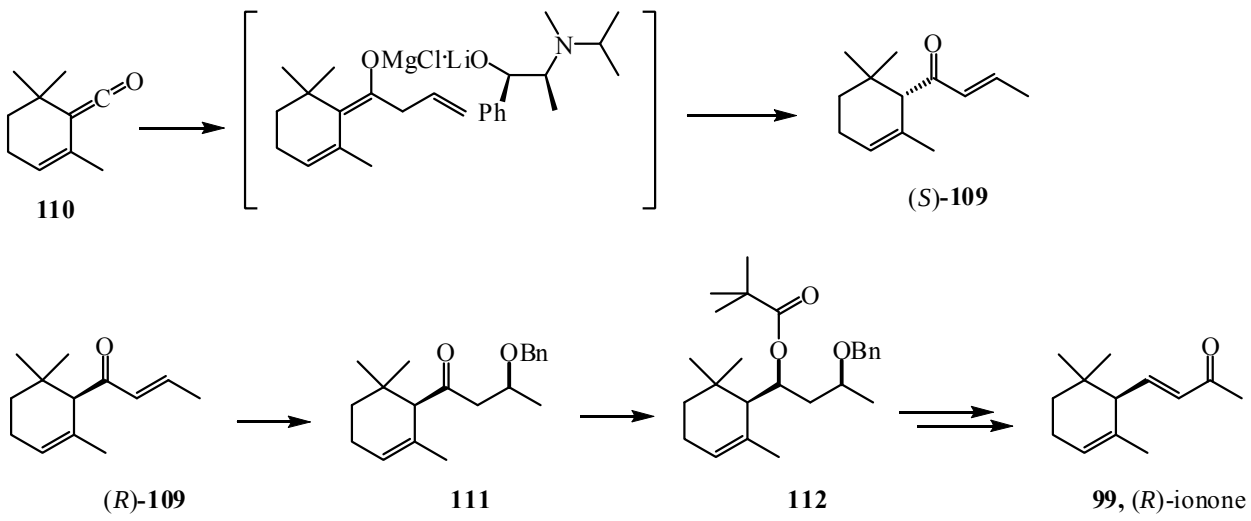
The synthesis of an isomeric mixture of racemic α-ionone and β-ionone from citral **105** and acetone over CaO as a basic heterogeneous catalyst serves as an interesting example of using aldol condensations in organic synthesis of complex molecules (Scheme 3.2).[117]



Scheme 3.2. Synthesis of isomeric mixture of racemic α-ionone and β-ionone from citral and acetone.

The cyclization reaction proceeds by acid catalysis to form the carbocation **108**. Subsequent elimination of H^+ leads to the formation of a mixture of both α- and β-ionones.

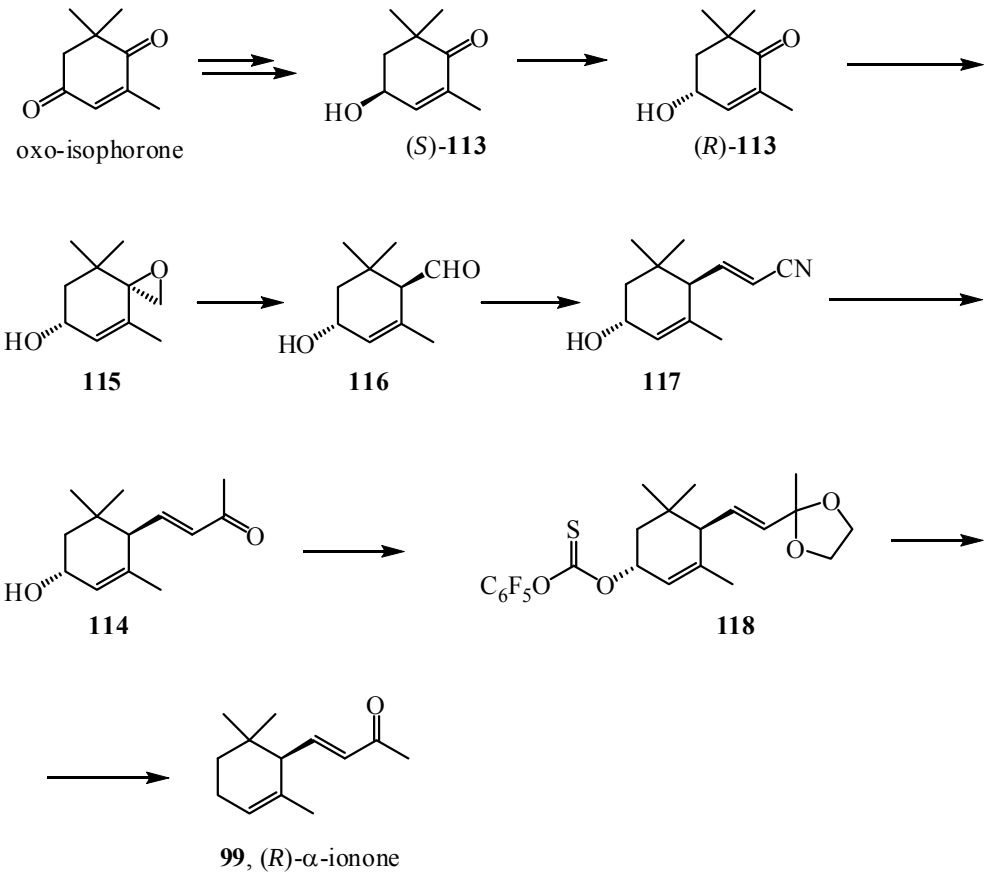
In order to prepare the pure α-ionone enantiomers for olfactory evaluation and for use as intermediates in the synthesis of other odorants, Fehr and Guntern[109] devised a method for the conversion of (*R*)- and (*S*)-α-damascone (**109**) into (*R*)- and (*S*)-α-ionone (**99** and **100**). Both enantiomers of **109** are accessible from ketene **110** by enantioselective protonation of an intermediate enolate (Fig 3.3).[109] Addition of allylmagnesium chloride to ketene **110** was performed in the presence of the lithium salt of (+)- or (–)-*N*-isopropylephedrine. Once the enolate had been formed, additional chiral auxiliary was added prior to quenching of the reaction with HCl, affording (*R*)-(+)- and (*S*)-(–)-**109**, respectively. Michael addition of benzyl alcohol in the presence of 1,1,3,3-tetramethylguanidine then permitted (*R*)-(+)-damascone [(*R*)-(+)-**109**] to be transformed into a 7:3 mixture of **111** and the starting material. Compound **111** was then reduced and esterified by treatment with LDA and *t*BuCOCl to afford pivalate **112**. This was subjected to debenzylation, Jones oxidation, and base-catalyzed thermal elimination [$N(C_2H_4OH)_3$, 140 °C] to provide (*R*)-(+)-α-ionone in 99% *ee* ($[\alpha]_D^{20}$ = +407 (*c* = 0.04, $CHCl_3$)). By the same procedure, (*S*)-(–)-damascone was transformed into (*S*)-(–)-α-ionone, also in 99% *ee* ($[\alpha]_D^{20}$ = –431, *c* = 0.035, $CHCl_3$).



Scheme 3.3. Fehr and Guntern's enantioselective synthesis of (*R*)- and (*S*)-α-ionone.

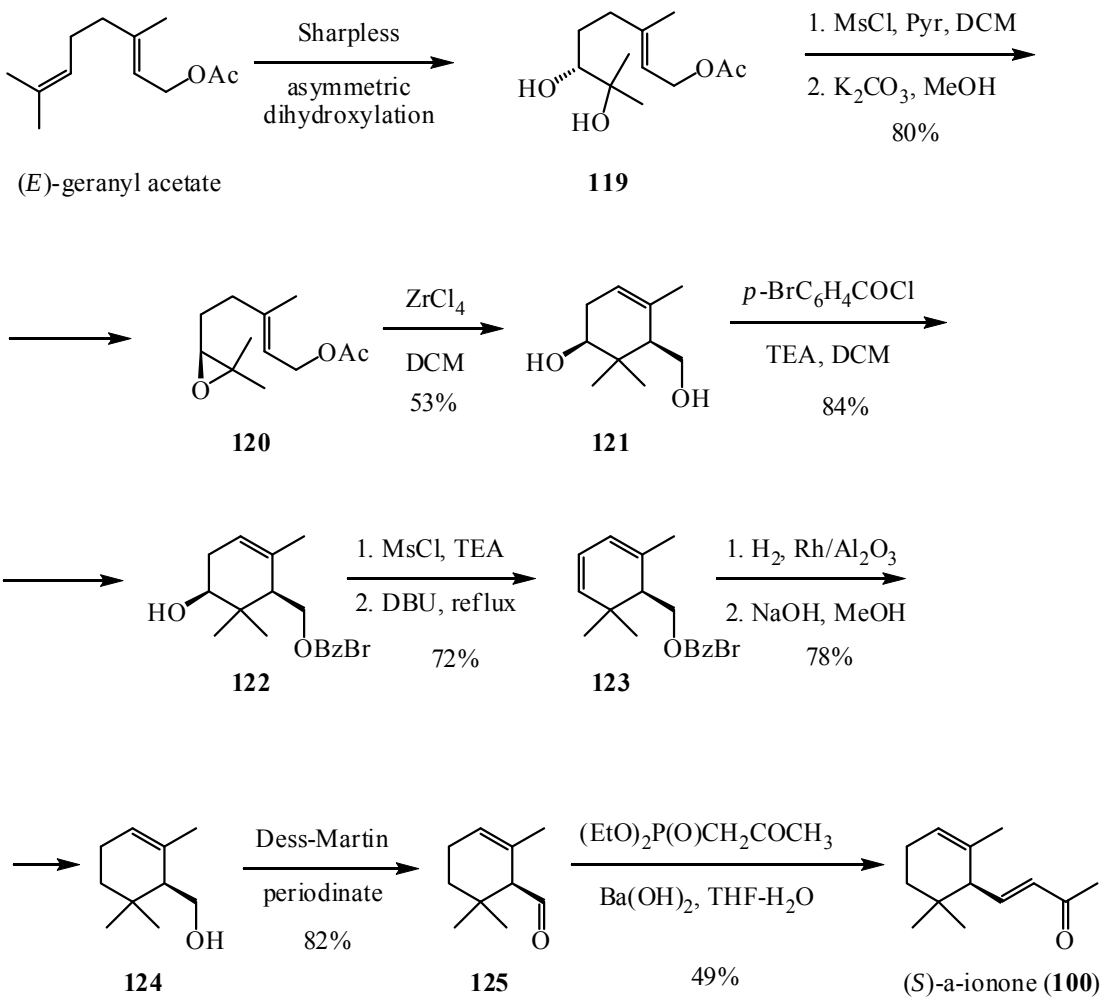
Pfander and Semadeni employed (*S*)-(−)-phorenol (**113**, 99% *ee*) as starting material in their synthesis of optically active (*R*)-(+)-α-ionone.[110] Compound (*S*)-**113** was prepared by a synthetic path involving Baker's yeast reduction of oxoisophorone[118] to produce an optically active starting material. This was then converted into (3*R*,6*R*)-3-hydroxy-α-ionone (*R*)-**113** according to a procedure by Mayer and Rüttimann (Scheme 3.4),[118] with the difference that the configuration at C-4 of (*S*)-**113** was inverted by a Mitsunobu reaction rather than by acetate displacement. The OH-group in (*R*)-**113** was protected and the carbonyl function was converted into an oxirane ring with dimethylsulfonium methylide. The resulting epoxide **115** was then stereoselectively opened with catalytic amounts of $Me_2EtCOMgBr$, to afford the unstable aldehyde **116**. A Wittig–Horner–Emmons reaction between compound **116** and diethylphosphonoacetonitrile afforded **117.** Alkylation with MeLi and subsequent hydrolysis/deprotection furnished hydroxyionone **114**. Reductive deoxygenation of the *O*-pentafluorophenyl thiocarbonate derivative **118** with Bu_3SnH and AIBN according to a

procedure reported by Barton[119] afforded (*R*)-(+)-α-ionone in 26% yield from **114**, after protection/deprotection of the carbonyl group. Despite the use of enantiomericly pure (*R*)-**113,** the prepared sample of (*R*)-(+)-α-ionone had an $[\alpha]_D^{20}$ value of only +345 (*c* = 0.52, EtOH), which corresponds to only 85% *ee*. By the same route, (*S*)-(−)-α-ionone was prepared from (*S*)-**113**, but with approximately 45% *ee* ($[\alpha]_D^{20}$ = −124, *c* = 0.32, EtOH).



Scheme 3.4. Pfander and Semadeni's enantioselective synthesis of (*R*)- and (*S*)-α-ionone.

The other original access to (*S*)-(−)-α-ionone is summarized in Scheme 3.5 where the strategic intermediate **121** was readily obtained by $ZrCl_4$-promoted stereospecific and regioselective biomimetic cyclization of (*S*)-(−)-geraniol epoxide **120**.[120]

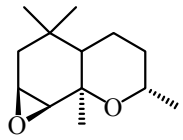


Scheme 3.5. Virdi's enantioselective synthesis of (*S*)-α-ionone.

It is noteworthy that all of these enantioselective synthetic approaches suffer from the same drawbacks. Only moderate yields of the desired ionone molecules are observed, while the procedures described above are quite laborious and expensive. The use of the combination of

reductive lithiation of alkyl sulfides and copper (I) catalyzed organozinc γ-allylic substitutions is able to eliminate those drawbacks and maintain equally high enantioselectivity.

The enantiomer of (*R*)-(+)-dihydro-α-ionone **95** was isolated from costus root oil (*Aplotaxis lappa* Decaisne, *Sassaurea lappa* Clarke) with a reported $[\alpha]_D^{20} = +167$[121] and from violet flower oil, with a reported $[\alpha]_D^{20} = +160$.[122] A sample of (*R*)-(+)-dihydro-α-ionone **95** with only 17% *ee* ($[\alpha]_D^{20} = +24.9$, *c* = 0.555, EtOH) was obtained by Francke et al. by selective hydrogenation of a (*R*)-α-ionone sample of 18.7% *ee* with Pd/C in alkaline solution.[123] It was used as an intermediate in the synthesis of epoxytetrahydroedulan **S1** (Scheme 3.6), a terpenoid from the hairpencils of *Euploea* (Lep: Danainae) butterflies.[123]

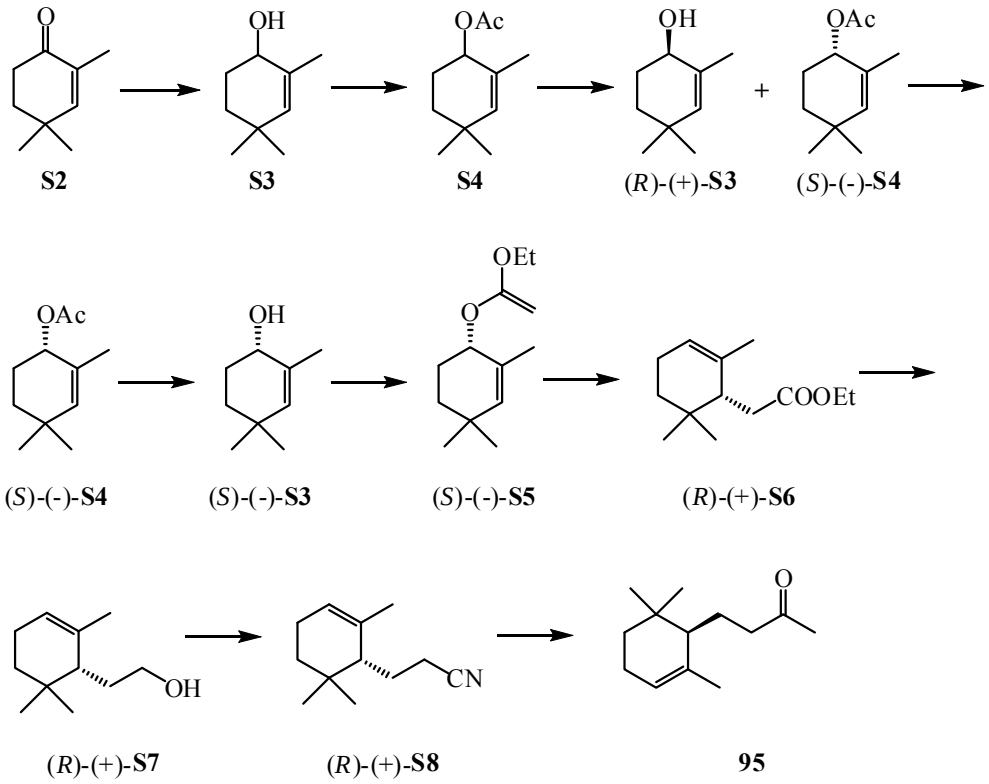


S1

Scheme 3.6. Epoxytetrahydroedulan.

In 1991, Mori et al. described the conversion of the chiral building block (*S*)-(-)-**S3** into enantiomericly pure (*R*)-(+)-dihydro-α-ionone **95** (Scheme 3.7).[124] 2,4,4-Trimethyl-2-cyclohexenone (**S2**) was reduced with either LAH or $NaBH_4/CeCl_3$ to provide (±)-**S3**, which was acetylated to give (±)-**S4** and submitted to enzymatic hydrolysis. PLE treatment in 0.1 M phosphate buffer with 20% MeOH at pH = 7.5 afforded (*R*)-(+)-**S3** (100% *ee*) and (*S*)-(-)-**S4** (41% *ee*) after 65.5 h at -10 °C. The enantiomeric excess of acetate (-)-**S4** was increased to 100% by means of a further PLE hydrolysis, followed by crystallization of the corresponding 3,5-dinitrobenzoate derivative. An *ortho*-ester Claisen rearrangement of (-)-**S5** provided (+)-**S6**,

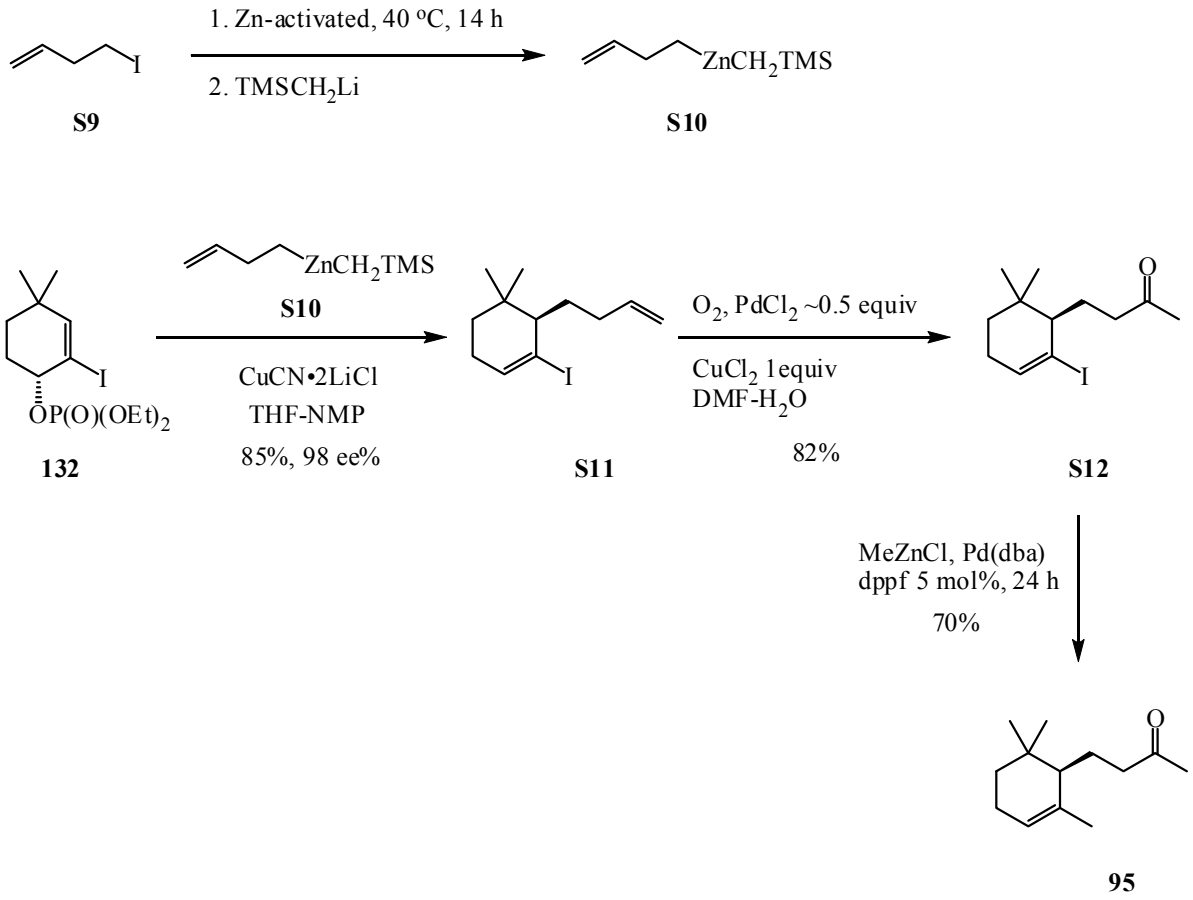
which was reduced with LAH to (+)-**S7**. This last compound was elongated by one carbon atom by cyanide substitution of the tosylate. A Grignard reaction between the resulting nitrile (*R*)-(+)-**S8** and MeMgI provided, after acidic workup, (*R*)-(+)-dihydro-α-ionone **95** with an $[\alpha]_D^{20}$ = + 138.4, *c* = 0.615, EtOH (Scheme 3.7).[124]



Scheme 3.7. Mori's enantiomeric synthesis of pure (*R*)-(+)-dihydro-α-ionone **95**.

Recentely, Knochel and co-workers reported an enantioselective synthesis of (*R*)-(+)-dihydro-α-ionone **95** using the copper cyanide mediated γ-allylic substitution reaction of a mixed dialkylzinc reagent **S10** with allylic diethylphosphate **132** as a key step (Scheme 3.8).[125] The desired mixed dialkylzinc reagent **S10** was prepared by the reduction of 4-iodobutene-1 with

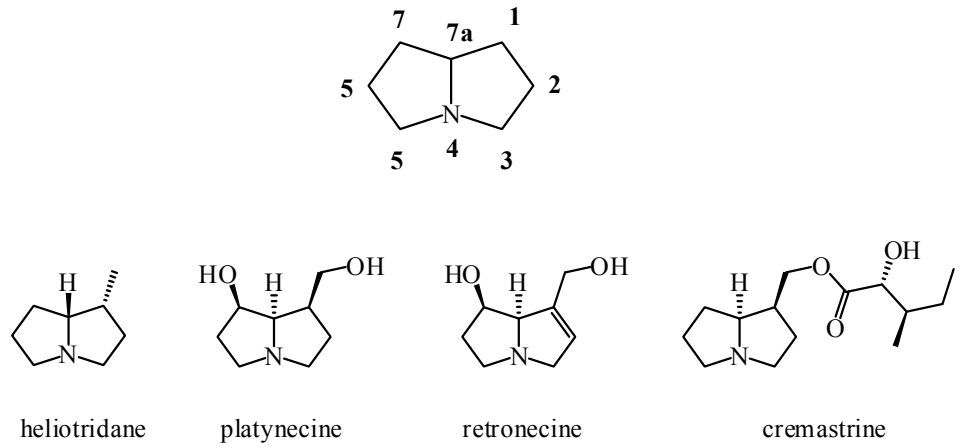
activated zinc foil at 40 °C in 14 h controlled by GC, followed by the addition of the Peterson reagent $TMSCH_2Li$. Although the γ-allylic substituted product **S11** was obtained in good yield, the "dummy ligand" $TMSCH_2$- is wasted during the reaction (Scheme 3.8). Moreover, the large amount of CuCN•2LiCl (1 equiv) used in the synthesis of **S11** requires special caution due to the high risk of environmental hazard. The intermediate product was then converted into (*R*)-(+)-dihydro-α-ionone **95** ($[\alpha]_D^{20}$ = + 149.5, *c* = 0.55, EtOH) in two steps including Pd-catalyzed oxidation and Negishi coupling on Pd(dba) in the presence of the dppf ligand (Scheme 3.8). Unfortunately, it is necessary to note, that the description of the ^{13}C NMR spectrum of (*R*)-(+)-dihydro-α-ionone **95** given in Knochel's paper[125] is partially incorrect. The correct one can be found elsewhere, for instance in Mori's paper.[124]



Scheme 3.8. Knochel's enantiomeric synthesis of (*R*)-(+)-dihydro-α-ionone **95**.

3.1.2 Pyrrolizidine Alkaloids.

Pyrrolizidines are widespread alkaloids produced by plants. Many of these pyrrolizidines are known in the form of hydroxylated derivatives, and are usually substituted at the 1- and/or 7-positions.[126,127] Due to potent biological activity and because of extensive opportunities for stereochemical variations within the bicyclic framework, these bases have emerged as attractive targets for the development of new synthetic methodology.[128] Typical examples of these bases are given in Scheme 3.9



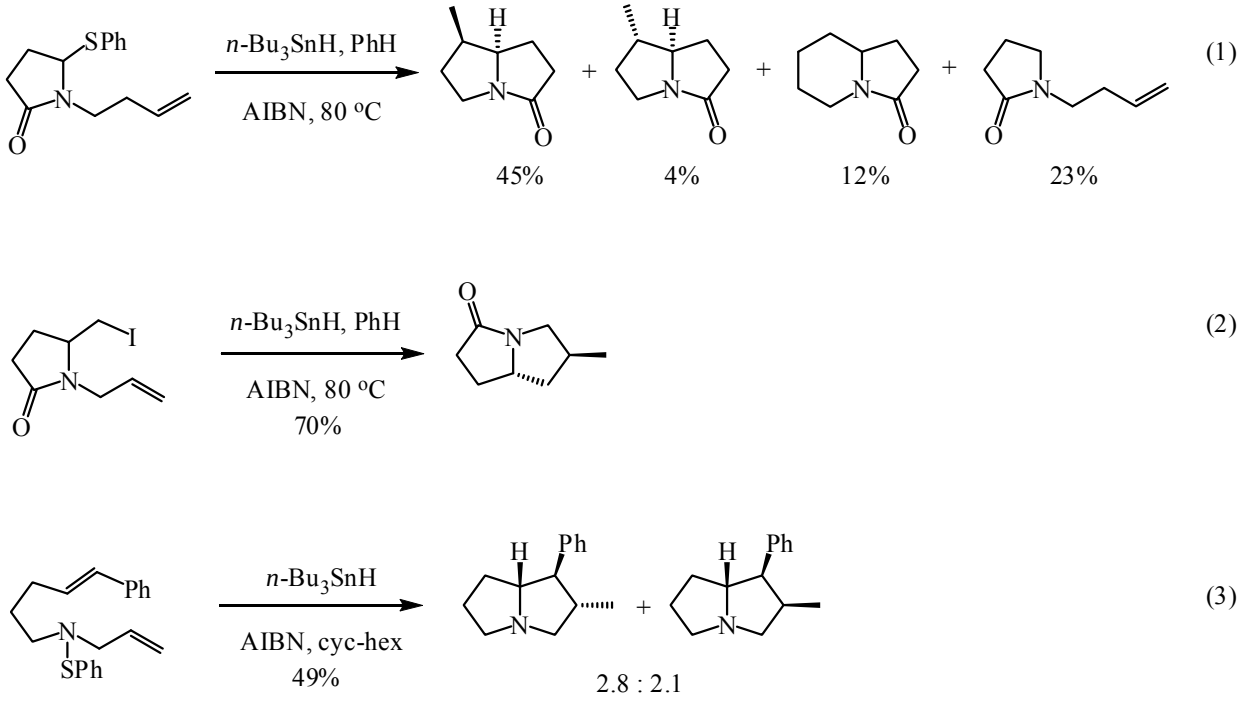
Scheme 3.9. Representative pyrrolizidine alkaloids.

The formation of the pyrrolizidine bicyclic core generally occurs by cyclization of a conveniently substituted pyrrolidine moiety. One popular strategy that has been exploited, regardless of the methodology highlighted, involves the preparation of the bicyclic framework as a pyrrolizidin-3-one, which can be subsequently reduced to the necine base (3-hydroxy pyrrolizidine). Methods to form the alkaloid framework are quite varied and include acylimmium cyclizations,[129,130,131] ionic cyclizations,[132] carbene insertion,[133] anodic oxidation,[134] intramolecular amination/cyclization,[135] metal-catalyzed atom transfer cyclizations,[136] sequential aza-ene reaction and allylsilane-hydrazonium ion ring closure[137] and olefin cyclization.[138]

Some of the earliest reported syntheses of pyrrolizidines employed harsh, two-step catalytic hydrogenation methods for the cyclization of the corresponding γ-nitropilemic esters.[139]

The most abundantly used technique for synthesis of the pyrrolizidinone framework, employs generation and cyclization of amino radicals. Hart was the first who focused on the use of this type of cyclizations for alkaloid synthesis.[140] Among a number of α-substituted lactams, sulfides (Scheme 3.10, Eq. 1) and iodides were chosen as the most suitable starting material for

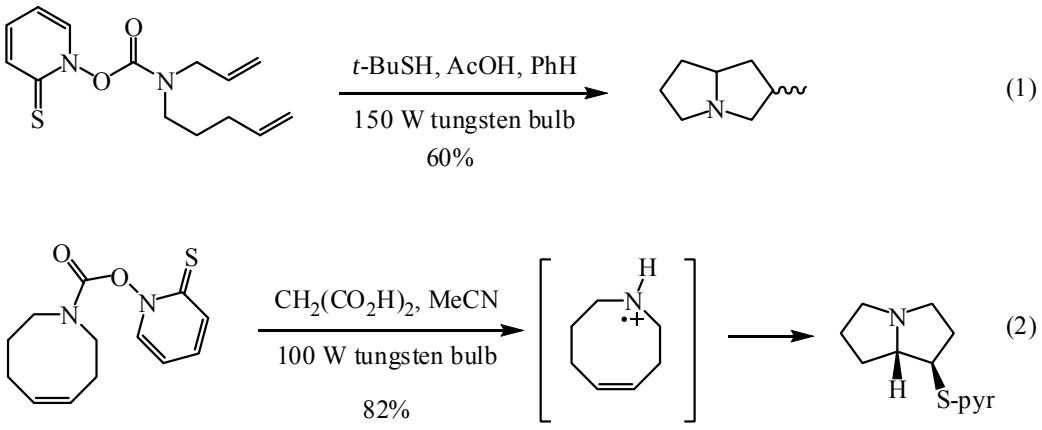
the tributyltin hydride mediated reactions. However, while iodides have never been readily available and satisfactorily stable, the sulfides used for the cyclization led to a complex mixture of products. The use of chiral building blocks, such that the original stereogenic center can be retained and impart diastereoselectivity during the radical cyclization, was employed by several groups (Scheme 3.10, Eq. 2).[141,142] Bowman and co-workers utilized aminyl radicals originating from sulfenamides and tributyltin hydride, to complete tandem cyclizations that resulted in moderate yields (Scheme 3.10, Eq. 3).[143]



Scheme 3.10. Radical cyclizations to generate the pyrrolizidinone skeleton.

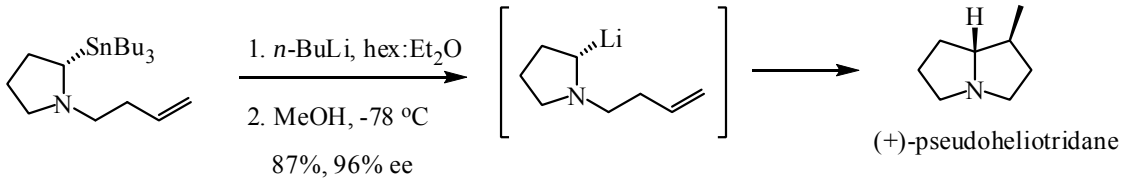
Utilizing *N*-hydroxypyridine-2-thione carbamates (PTOC carbamates) as precursors for aminium cation radicals, Newcomb and co-workers explored both tandem (Scheme 3.11, Eq. 1)

and single intramolecular cyclizations (Scheme 3.11, Eq. 2) to form the pyrrolizidine framework.[144]



Scheme 3.11. PTOC carbamates as precursors for aminium cation radicals.

It was Coldham who first successfully applied intramolecular carbolithiation and tin-lithium exchange in the preparation of the pyrrolizidine alkaloid (+)-pseudoheliotridane (Scheme 3.12).[145] This anionic cyclization gave a single diastereomer, due to its preference for reaction via a chairlike conformation. This is in contrast to the related radical cyclizations that are known, which can give a variety of products.

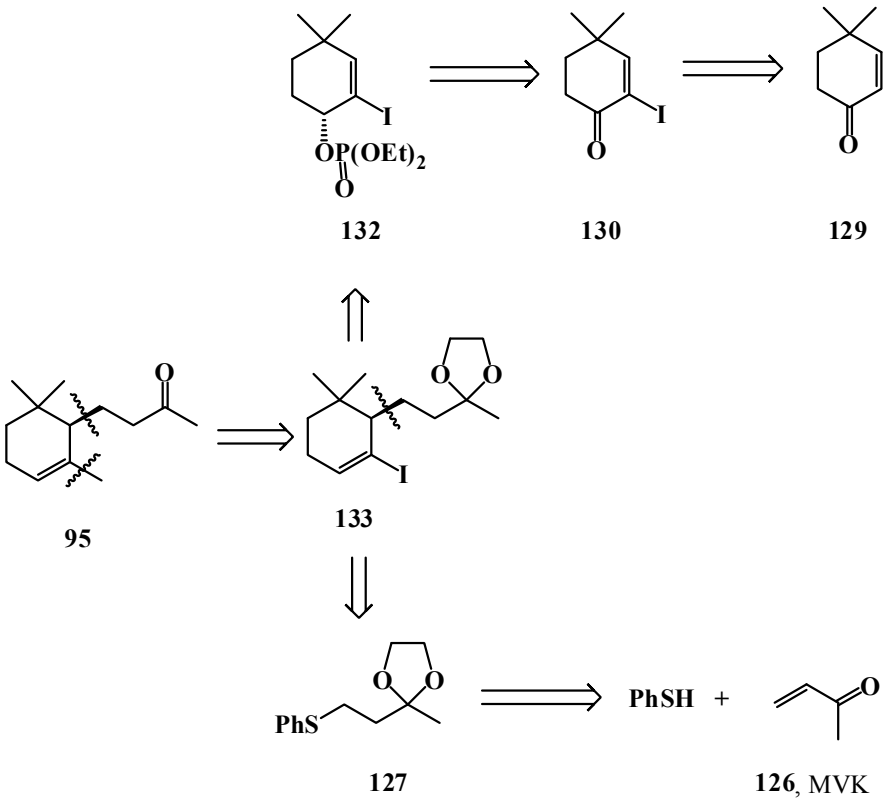


Scheme 3.12. Anionic cyclizations employed by Coldham to form a pyrrolizidine skeleton.

3.2 RESULTS AND DISCUSSION

3.2.1 Enantioselective Synthesis of (*R*)-dihydro-α-ionone

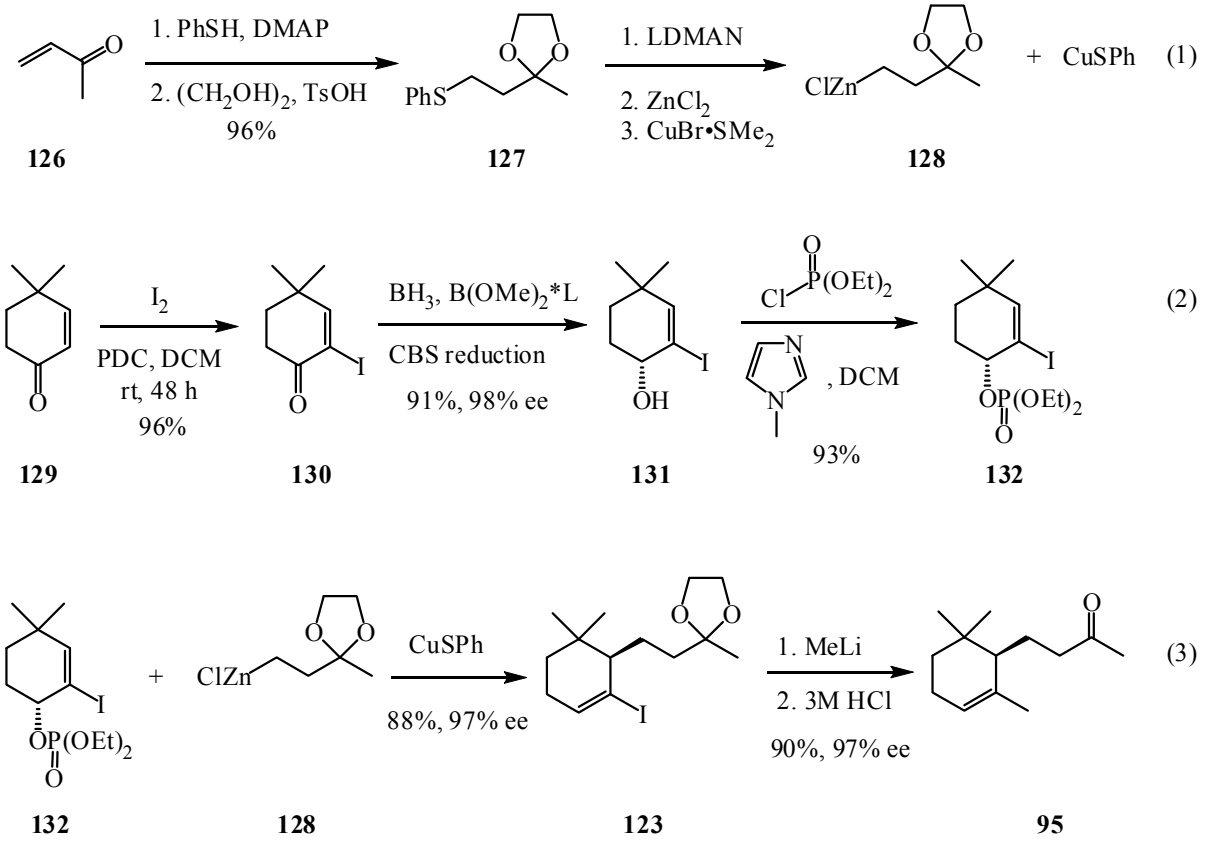
The remarkable ability of monoalkylzincs to undergo regio- and *anti*-selective γ-allylic substitution reactions even with sterically hindered substrates is demonstrated by the preparation of (*R*)-dihydro-α-ionone **95**. Scheme 3.13 shows the retrosynthetic analysis starting from cheap and readily available methyl vinyl ketone (MVK, **126**), thiophenol and 4,4-dimethyl-2-cyclohexenone **129**.



Scheme 3.13. Retrosynthesis of (*R*)-(+)-dihydro-α-ionone **95**.

When our work on **95** was in progress, a paper by Knochel[125] appeared in which a key step was also a γ-allylic substitution using the same substrate **132** (see Scheme 3.8). There are several major differences between his execution and ours of the synthesis of (*R*)-(+)-dihydro-α-ionone **95**. These are summarized in the Conclusions section of this chapter.

Scheme 3.14 represents the enantioselective approach to **95**. The strategic intermediate **131** was readily obtained by enantioselective Corey-Bakshi-Shibata reduction[146] of 1-iodo-4,4-dimethyl-2-cyclohexanone **130**, which is readily available from commercial 4,4-dimethyl-2-cyclohexanone **129**. The hydroxyl group in **131** was then converted into the good phosphate leaving group (Scheme 3.14, Eq. 2).



Scheme 3.14. Enantioselective synthesis of (*R*)-dihydro-α-ionone **95**.

The direct iodination of the ketone **129** with iodine requires the presence of a base, such as pyridine, and an oxidizing agent. Pyridinium dichromate, always containing a catalytic amount of free pyridine, is recommended as a combination of both.[147] While the role of pyridine is to eliminate HI after the iodine addition to the double bond of the enone **129**,[148] dichromate anion oxidizes HI formed during elimination back to iodine to make the whole iodination process irreversible.[147]

The desired alkylzinc reagent **128** was prepared by reductive lithiation of the corresponding alkyl sulfide **127** with LDMAN, followed by transmetallation with $ZnCl_2$ and addition of one full equivalent of $CuBr{\bullet}SMe_2$, which was needed to seize the other very strong nucleophile SPh^- (Scheme 3.14, Eq. 1). Subsequentely, that very CuSPh precipitate was further used in the reaction as the actual form of the copper(I) catalyst.

The product **133** was prepared by the addition of the phosphate **132** directly to the reaction mixture containing alkylzinc reagent **128** and CuSPh at ambient temperature. When the reaction was finished, DMAN was completely carefully removed by washing with an almost stoichiometric amount of 1 M HCl in a separatory funnel in order to not damage the dioxolane protecting group in **133**.

The iodo-functional group in compound **133** was quantitatively replaced by a methyl group in the reaction with one equivalent of MeLi at -78 °C and then the dioxolane protecting group was removed by 3 M HCl.

The alkyl sulfide **127** is readily prepared from commercially available MVK and thiophenol[149] followed by protecting the keto-group with ethylene glycol under acidic conditions.[150]

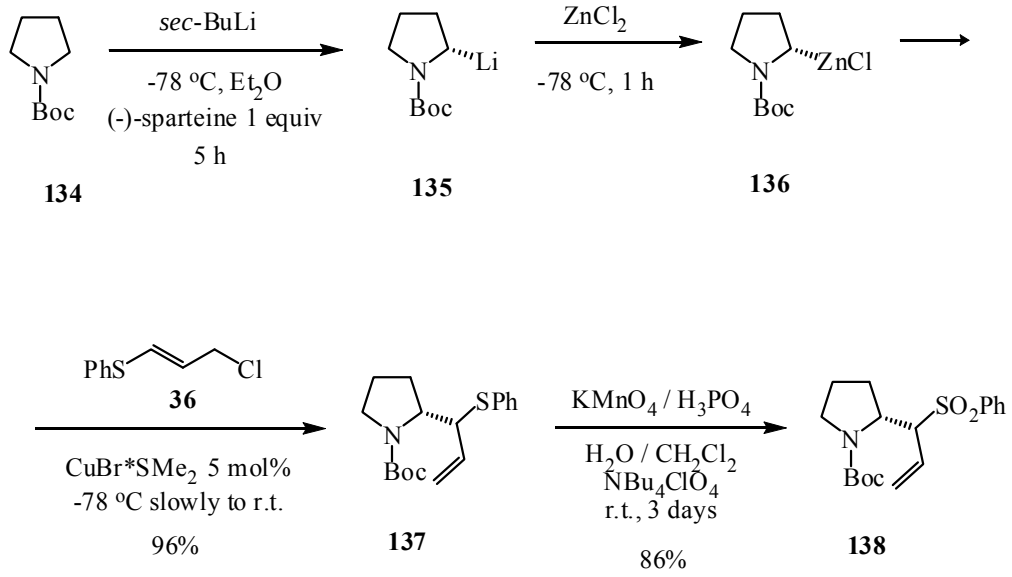
Thus, the combination of reductive lithiation and a copper catalyzed organozinc γ-allylic substitution reaction has allowed us to develop an efficient and simple highly enantioselective synthesis of (*R*)-(+)-dihydro-α-ionone with very high overall yield (68%, 97% ee by capillary GC, ($[\alpha]_D^{24}$ = + 140.58, *c* = 0.090, CH_2Cl_2: literature[124] $[\alpha]_D^{20}$ = + 138.4, *c* = 0.615, EtOH). It has been also demonstrated that monoalkylzincs produced by reductive lithiation of the corresponding alkyl sulfides can be successfully used in regio- and stereoselective syntheses of natural products.

3.2.2 A Novel Synthetic Approach to a Potential Precursor of the Pyrrolizidine Framework.

The well defined reaction conditions for copper catalyzed alkylzinc γ-substitutions that we have developed and described in Chapter 1 were next exploited in a pyrrolizidine synthesis.

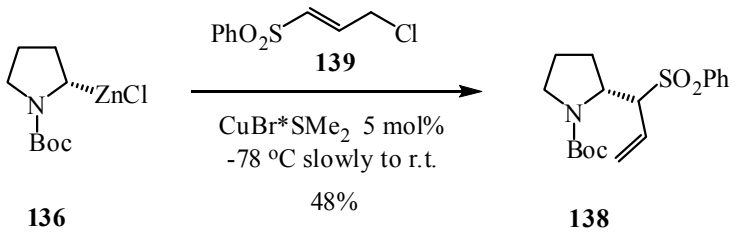
Stereoselective lithiation of a Boc-protected pyrrolidine **134** in the presence of the chelating agent (-)-sparteine is a well known reaction and can be performed enantioselectively in almost quantitative yield[151] in Et_2O, as shown in Scheme 3.15. Lithium organic **135** formed by Beak's procedure was transmetallated with 1 equiv of $ZnCl_2$ to form organozinc reagent **136**,[152] which was immediately subjected to the copper(I) catalyzed γ-S_{AL} reaction with **37**, forming exclusively the product of γ-substitution **137**, which was obtained crude in nearly quantitative yield as a 1:1 mixture of two diastereomers (Scheme 3.15) and used in the next step without further purification; alternatively **137** can be purified using 15% EtOAc/hexane as eluent by silica chromatography. The product **137** was oxidized by $KMnO_4$ in H_3PO_4 water/DCM solution in the presence of phase-transfer catalyst NBu_4ClO_4 for 3 days at ambient temperature.[153] All

attempts to oxidize the sulfide **137** with MCPBA in DMC failed, probably, due to the high acidity of MCPBA by-product 3-chlorobenzoic acid. It is assumed that these acids were able to remove the Boc-protecting group and the secondary amine formed was immediately oxidized. The very low solubility, if any, of H_3PO_4 in the organic phase was the necessary advantage over AcOH usually employed in such oxidizing protocols and allowed the avoidance of deprotection.



Scheme 3.15. Synthesis of highly functionalized Boc-protected pyrrolidine by copper catalyzed γ-substitution.

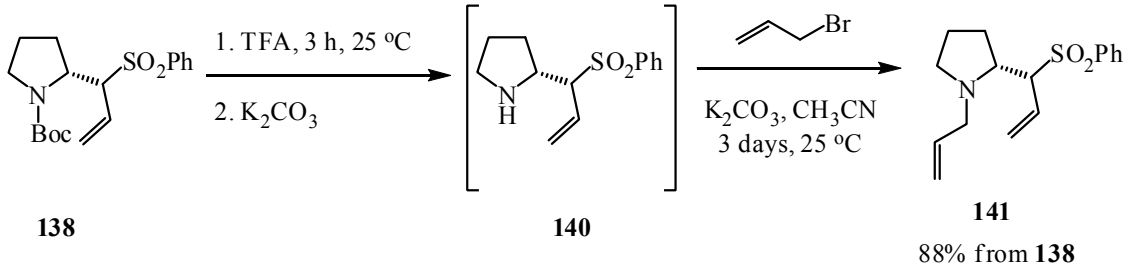
It is noteworthy that the organozinc **136** is able to react with the sulfonyl derivative **139**, but only in moderate yield (Scheme 3.16). Since other hindered organozinc halides are capable of this γ-allylic substitution in very good yields (see Chapter 1), the decreased yield is probably due to the extra steric hindrance provided by the Boc group.



136 138

Scheme 3.16. Reaction between the organozinc **136** and the sulfonyl derivative **139** goes in a moderate yield.

Deprotection of **138** with TFA followed by processing in saturated aqueous K_2CO_3,[154] led to the formation of free pyrrolidine **140** (Scheme 3.17). Compound **140** was found to be unstable in air and was immediately allylated, without further purification, by allyl bromide in the presence 4 equiv of K_2CO_3 in CH_3CN at room temperature for 3 days under an argon atmosphere to produce N-allylpyrrolidine **141** as a 1:1 mixture of two diastereomers (Scheme 3.17).

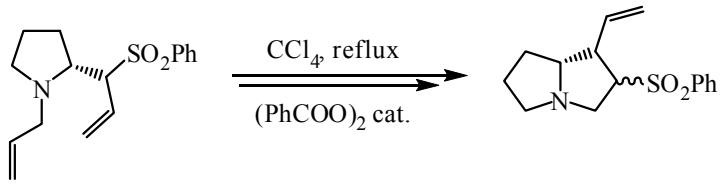


138 140 141

88% from **138**

Scheme 3.17. Preparation of the substrate for further cyclization reaction.

The product **141** is a possible cyclization substrate either by a Pd-catalyzed zinc-ene cyclization reaction[155] or by radical cyclization, known for allyl sulfones[156] (Scheme 3.18) and which would lead to a mixture of diastereomers.



141

Scheme 3.18. Proposed further radical cyclization of the sulfonyl containing pyrrolidine **141** into a mixture of diastereomeric pyrrolizidines.

3.2.3 Conclusions

In the present work, we have demonstrated the remarkable ability of monoalkylzincs to undergo regio- and enantioselective γ-allylic substitutions even with sterically hindered substrates by the enantioselective synthesis of the natural fragrance (*R*)-(+)-dihydro-α-ionone **95** in very high overall yield and enantioselectivity. The synthesis reported in this work exploits significant advantages of reductive lithiation of alkyl phenyl sulfides by LDMAN radical-anion reagent and γ-allylic substitution reactions of alkylzinc halides catalyzed by a copper phenyl sulfide. It is more effective and simpler than the earlier synthesis of **95** reported by Mori.[124] It also compares well with the Knochel synthesis,[125] which was published while our synthetic endeavor was in progress. Although our synthesis and that of Knochel are comparable in length, ours results in the conversion of the common intermediate **132** to **95** in 64% yield while Knochel's yield for this conversion is 49%. Furthermore, ours avoids the long and complex reductive zincation using activated zinc foil and 4-iodo-1-butene controlled by GC, the use of an

expensive Petersen reagent $TMSCH_2Li$, which is wasted during the reaction, the use of a large amount of hazardous CuCN•2LiCl, and two steps using Pd catalysis.[125]

Furthermore, it was shown that a γ-allylic substitution reaction between a pyrrolidinylzinc halide and an allylic chloride, bearing another suitable functionality at the vinyl group, can be utilized as a method for pyrrolizidine synthesis that promises to be simpler and shorter than extant methods. Although significant efforts have been made in this area, it is still necessary to further optimize reaction conditions as well as reactive allylic substrates.

3.3 EXPERIMENTAL SECTION

Instrumentation. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C at 22°C. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of the $CDCl_3$ triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). Coupling constants, J, are reported in Hz. High resolution mass spectra were recorded on a CH-5 double focusing Varian MAT or on VG 70-SE mass spectrometer.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium metal in the presence of benzophenone as indicator. Hexane and dichloromethane were distilled over CaH_2.

General Experimental Procedures. All reactions were carried out under a positive pressure of dry argon gas in oven-dried (140 °C) flasks and standard precautions against moisture were taken. Flash column chromatography (low pressure) was performed with Silicycle Silia-P Flash silica gel (40-63 μm, surface area – 500 m^2/g) or with Sigma-Aldrich basic aluminum oxide (150 mesh, 58 Å, activated). Thin-layer chromatography was performed on glass supported 250 μm silica GF plates (Analtech). Visualization of TLC plates was accomplished either with 254 nm UV light or with an aqueous solution of $KMnO_4$ (1%) with NaOH (1%) and K_2CO_3 (6%). A dry ice/acetone bath was used to obtain temperatures of –78 °C. An ice bath was used to obtain 0 °C. Anhydrous magnesium sulfate was used as the drying reagent. Enantiomeric purity was determined by chiral capillary GC analysis in TransForm Pharmaceuticals, Inc (a member of the Johnson & Johnson family of companies). In all cases, the analysis was calibrated with a sample of the racemate.

Capillary GC:

column : Chiraldex B-PH, 30.0 mm x 0.25 mm

method A: 40 °C (3 min), ramp of 18 °C/min to 180 °C (100 min)

method B: 100 °C const.

(*R*)-dihydro-α-ionone (95).

A one neck round bottom neck was purged three times with argon gas and charged with 60 mL of dry THF and 3.36 g (9.6 mmol) of **133**. The reaction mixture was cooled to -78 °C and 6.3 mL of a 1.6 M ethereal solution of MeLi (10.0 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h and then at -25 °C for 1 h. The reaction was quenched with brine solution. The organic product was extracted with ether and the extract was washed with

200 mL of 3 M HCl for 24 h at ambient temperature and then the product was extracted with ether (3×50 mL). The extract was washed with saturated aqueous K_2CO_3 and with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (15% EtOAc/hexane) to afford 1.66 g (90% yield) of the titled (*R*)-dihydro-α-ionone **95** ($[\alpha]_D^{24}$ = + 140.58, *c* = 0.090, CH_2Cl_2). GC (method B): t_R/min = 45.60 (minor), 49.14 (major); 97% *ee*. ^{1}H NMR ($CDCl_3$), δ (ppm): 5.35 – 5.30 (s, broad, 1 H), 2.50 – 2.44 (m, 2 H), 2.13 (s, 3 H), 1.98 – 1.96 (broad, 2 H), 1.82 – 1.74 (m, 1 H), 1.67 (s, 3 H), 1.64 – 1.56 (m, 1 H), 1.49 – 1.36 (m, 2 H), 1.17 – 1.10 (m, 1 H), 0.92 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 208.6, 135.3, 120.8, 48.2, 43.5, 32.3, 31.3, 29.7, 27.4, 27.3, 24.1, 23.3, 22.8. These NMR spectra agreed well with the description of Mori's spectra[124] and with the actual spectra provided by Knochel.[125] Exact mass calcd. for $C_{13}H_{22}O$ 194.1671, found 194.1668.

4-Phenylthio-2-butanone.[157]

A three neck round bottom flask under argon atmosphere was charged with 30 mL of dry dichloromethane, 1.1 g (9.3 mmol) of DMAP and 5 mL (42.1 mmol) of thiophenol. A solution of 3.8 mL (46.3 mmol) of methyl vinyl ketone (MVK, **126**) in 5 mL of CH_2Cl_2 was added dropwise by using a syringe pump at room temperature. The reaction mixture was stirred for 24 h at ambient temperature and then the reaction was quenched in 240 mL of 5% HCl. The product was extracted with dichloromethane and the organic extract was washed with a saturated solution of K_2CO_3, followed by a brine solution and dried over $MgSO_4$. The organic solvents were removed by rotary evaporation to afford 8.9 g (ca. 100% yield) of 4-phenylthio-2-butanone as a crude but essentially pure pale yellow oil. The product was used without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.33 – 7.15 (m, 5 H), 3.11 (t, 2 H, *J* = 7.0 Hz), 2.73 (t,

2 H, J = 7.0 Hz), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 206.4, 135.5, 129.2, 128.8, 126.1, 42.8, 29.9, 27.2.

2-Methyl-2-(2-(phenylthio)ethyl)-1,3-dioxolane (127).

Crude 4-(phenylthio)butan-2-one (8.9 g, ~50 mmol) was added at ambient temperature to a solution of ethylene glycol (21.0 mL, 347 mmol) and trimethyl orthoformate (TMOF, 17.0 mL, 148 mmol) and then a catalytic amount of *p*-TsOH (10 mol%, 0.6 g) was added in one portion. After being stirred for 5 h, the mixture was diluted with 100 mL of Et_2O and the reaction was quenched with 200 mL of a saturated aqueous solution of K_2CO_3. The product was extracted with ether, and the extract was washed with 250 mL of deionized water and then dried over $MgSO_4$. The extract was concentrated in vacuo and the crude residue was chromatographed over silica gel (20% EtOAc/hexane) to afford 9.1 g (96% yield starting from thiophenol and MVK (**126**)) of the titled product **127**. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.32 – 7.11 (m, 5 H), 3.92 – 3.81 (m, 4 H), 2.99 – 2.94 (m, 2 H), 2.00 – 1.95 (m, 2 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 136.4, 138.6, 138.2, 125.3, 108.8, 64.4, 38.5, 27.3, 23.7; exact mass calcd. for $C_{12}H_{16}O_2S$ 224.0871, found 224.0871.

2-Iodo-4,4-dimethyl-2-cyclohexenone (130).

A flame dried 250 mL round bottom flask was charged with 5.0 g (40 mmol) of 4,4-dimethyl-2-cyclohexenone (**129**) and 120 mL of dry CH_2Cl_2. Pyridinium dichromate (PDC, 4.5 g, 12 mmol) and iodine (10.2 g, 40 mmol) were added consecutively and the reaction mixture was stirred for 25 h at room temperature. Iodide (2.0 g, 8 mmol) was added and the reaction mixture was stirred for 24 h at ambient temperature and was filtered through a celite pad and the

precipitate was washed with 200 mL of pentane. The combined filtrate was washed with 100 mL of 2 M HCl, followed by 100 mL of a saturated water solution of K_2CO_3 and with a saturated water solution of $Na_2S_2O_3$, and dried over $MgSO_4$. The organic solvents were removed by rotary evaporation to afford 9.6 g (96% yield) of a crude but essentially pure product **130**, which was used without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.48 (s, 1 H), 2.68 (t, 2 H, J = 6.8 Hz), 1.95 (t, 2 H, J = 6.8 Hz), 1.22 (s, 6 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 191.1, 167.4, 101.4, 37.5, 35.4, 32.8, 26.9; exact mass calcd. for $C_8H_{11}IO$ 249.9854, found 249.9849.

(*R*)-2-Iodo-4,4-dimethylcyclohex-2-enol (131).

A flame dried 250 mL round bottom flask was purged three times with argon gas and charged with 50 mL of dry THF, 0.51 g (5.0 mol%, 2.0 mmol) of *L*-diphenylprolinol and 0.23 mL (5.0 mol%, 2.0 mmol) of $B(OMe)_3$. The mixture was stirred for 1 h at room temperature and then 6.80 mL (38.2 mmol) of borane-N,N-diethylaniline complex was added via a syringe. A solution of 9.56 g (38.2 mmol) of 2-iodo-4,4-dimethyl-2-cyclohexenone (**130**) in 20 mL THF was added dropwise in about 1 h by syringe pump. The reaction mixture was stirred for 2 h and the reaction was carefully quenched with 20 mL of methanol. Organic solvents were removed by rotary evaporation. The residue was dissolved in ether and washed with 100 mL of a saturated solution of K_2CO_3 and then with a 10% aqueous solution of $KHSO_4$. The organic extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (20% EtOAc/hexane) to afford 8.72 g (91% yield) of the desired product **131** as a colorless oil ($[\alpha]_D^{22}$ = + 49.70, c = 0.058, CH_2Cl_2). GC (method A): t_R/min = 36.02 (minor), 43.54 (major); 98% *ee*. ^{1}H NMR ($CDCl_3$), δ (ppm): 6.21 (s, 1 H), 4.16 – 4.11 (broad, 1 H), 3.21 (d, 1 H, J = 6.0 Hz), 2.07 – 1.28 (m, 1 H), 1.92 – 1.83 (m, 1 H), 1.69 – 1.60

(m, 1 H), 1.52 – 1.43 (m, 1 H), 1.03 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 149.6, 102.3, 71.3, 36.8, 31.8, 28.8, 28.5, 27.7; exact mass calcd. for $C_8H_{13}IO$ 252.0011, found 252.0004.

(*R*)-Diethyl 2-iodo-4,4-dimethylcyclohex-2-enyl phosphate (132).

To a solution of 12.0 mL (83 mmol) of diethyl chlorophosphate and 9.0 mL (110 mmol) of methylimidazole in 150 mL of dry dichloromethane at 0 °C was added dropwise a solution of 13.9 g (55 mmol) of (*R*)-2-iodo-4,4-dimethylcyclohex-2-enol (**131**) in 20 mL of dry CH_2Cl_2. The reaction mixture was stirred for 24 h at room temperature and the reaction was quenched with 200 mL of a pH 7.0 aqueous phosphate buffer solution (KH_2PO_4/Na_2HPO_4). The organic product was extracted with dichloromethane, dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (50% EtOAc/hexane) to afford 19.9 g (93% yield, mixture of several rotomers) of the titled product as a colorless oil, which crystallized slowly at 0 °C ($[\alpha]_D^{24}$ = + 32.37, *c* = 0.029, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 6.37 (s, 1 H), 4.84 – 4.78 (m, 1 H), 4.28 – 4.01 (m, 4 H), 2.13 – 2.04 (m, 2 H), 1.72 – 1.63 (m, 1 H), 1.54 – 1.46 (m, 1 H), 1.40 – 1.33 (m, 6 H), 1.05 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 152.8, 93.5, 77.6, 63.7, 36.9, 30.6, 28.8, 27.9, 26.8, 15.9. These NMR data agreed well with the literature values.[125] Exact mass calcd. for $C_{12}H_{22}O_4PI$ 388.0301, found 388.0285.

(*R*)-2-(2-(2-Iodo-6,6-dimethylcyclohex-2-enyl)ethyl)-2-methyl-1,3-dioxolane (133).

A solution of 4.10 g (18.3 mmol) of 2-methyl-2-(2-(phenylthio)ethyl)-1,3-dioxolane (**127**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (38.4 mmol) in 100 mL of THF at -78 °C. After being stirred for 30 min at that temperature to insure complete reduction, 18.5 mL (9.2 mmol) of a 0.5 M THF solution of $ZnCl_2$ was added and the

reaction mixture was stirred for 40 min at -78 °C. The acetone/dry-ice bath was then removed and the reaction mixture was allowed to warm to the ambient temperature and 4.00 g (19.2 mmol) of CuBr•SMe_2 was added in one portion at room temperature. After the mixture had been stirred for 10 min at the that temperature, a solution of 5.90 g (16.6 mmol) of (*R*)-diethyl 2-iodo-4,4-dimethylcyclohex-2-enyl phosphate (**132**) in 10 mL of TFH was added at room temperature. The reaction mixture was stirred for 36 h at ambient temperature and then the reaction was quenched with 200 mL of saturated aqueous K_2CO_3 and the mixture was filtered through a celite pad. The product was extracted with ether and the extract was washed in a separatory funnel with 1 M HCl (2×50 mL) and then again with 200 mL of saturated aqueous K_2CO_3. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (10% EtOAc/hexane) to afford 5.1 g (88% yield) of the titled product **133** as a pale yellow oil ($[\alpha]_D^{24}$ = + 63.26, *c* = 0.046, CH_2Cl_2). GC (method A): t_R/min = 44.12 (minor), 45.88 (major); 97% *ee*. ^{1}H NMR ($CDCl_3$), δ (ppm): 6.28 (t, 1 H, *J* = 3.0 Hz), 3.94 (s, 4 H), 2.10 – 1.97 (m, 3 H), 1.74 – 1.55 (m, 4 H), 1.52 – 1.44 (m, 1 H), 1.34 (s, 3 H), 1.25 – 1.19 (m, 1 H), 0.99 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 136.2, 109.7, 104.5, 64.4, 55.6, 37.9, 34.9, 30.2, 28.0, 27.5, 26.8, 25.7, 23.4; exact mass calcd. for $C_{14}H_{23}O_2I$ 350.0743, found 350.0727.

(*R*)-*tert*-Butyl-2-(1-(phenylsulfonyl)allyl)pyrrolidine-1-carboxylate (138), two step procedure.

To (-)-sparteine (3.60 mL, 15.0 mmol) and N-Boc-pyrrolidine **134** (1.70 mL, 10.0 mmol) in 40 mL of diethyl ether at – 78 °C was slowly added a 1.4 M hexane solution of *s*-butyllithium (8.60 mL, 12.0 mmol). The reaction mixture was stirred for 5 h at – 78 °C and then a 0.5 M THF solution of $ZnCl_2$ (24.0 mL, 12.0 mmol) was added. The reaction mixture was stirred for 1 h at

this temperature and then CuBr•SMe_2 (~5 mol%, 0.15 g) was added in one portion followed by the addition of 1-phenylthio-3-chloropropene **36** (1.85 g, 10.0 mmol). The resulting solution was allowed to warm slowly to room temperate overnight. The reaction mixture was poured into 200 mL of 5% phosphoric acid and insoluble precipitate was removed by filtration through a celite pad. The product was extracted with diethyl ether. The extract was washed with an aqueous solution of K_2CO_3, dried over $MgSO_4$ and concentrated in vacuo to afford 3.1 g (96% yield, a mixture of two diastereomers) of the crude product *tert*-butyl-2-(1-(phenylthio)allyl)pyrrolidine-1-carboxylate (**137**) as a 1:1 mixture of two diastereomers, which was used without further purification in the next stage. Elemental analysis: exact mass calcd. for $C_{18}H_{25}NO_2S$ 319.1606, found 319.1597.

To a solution of 2.80 g (8.5 mmol) of *tert*-butyl-2-(1-(phenylthio)allyl)pyrrolidine-1-carboxylate (**137**) and 0.5 g (~10 mol %) of ammonium perchlorate in 30 mL of methylene chloride in an ice-cooled 500 mL one-neck round-bottom flask were sequentially added a solution of 4.00 g (20.0 mmol) of potassium permanganate in 125 mL of water and 9.00 mL of concentrated (d = 1.74) phosphoric acid. After 3 days at ambient temperature, ca. 10 g of sodium bisulfite was added to decolorize the solution. The organic product was extracted with dichloromethane, and the extract was washed with saturated aqueous K_2CO_3, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (20% EtOAc/hexane) to afford 2.56 g (86% yield) of the titled product **138** as a 1:1 mixture of two diastereomers. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.90 – 7.82 (m, 2 H), 7.63 – 7.52 (m, 3 H), 5.93 (ddd, 1 H, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 9.9 Hz), 5.30 (d, 1 H, J = 9.9 Hz), 4.95 (d, 1 H, J = 17.1 Hz), 4.69 – 4.65 (broad, 0.5 H), 4.54 – 4.52 (m, 1 H), 4.24 – 4.21 (broad, 0.5 H), 3.46 – 3.43 (m, 1 H), 3.19 – 3.16 (m, 1 H), 2.42 – 2.36 (m, 1 H), 2.28 – 2.23 (m, 1 H), 1.88 – 1.81 (m, 2 H),

1.47 (s, 4.5 H), 1.41 (s, 4.5 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 153.8, 153.5, 138.6, 138.4, 133.6, 133.4, 128.8, 128.7, 128.6, 128.5, 126.4, 126.1, 125.6, 125.2, 80.0, 79.3, 70.4, 68.4, 55.8, 55.7, 46.9, 46.5, 28.4, 28.3, 27.3, 26.7, 24.3, 23.8; exact mass calcd. for ($C_{18}H_{25}NO_4S$ + Na) 374.1402, found 374.1397.

(*R*)-*tert*-Butyl-2-(1-(phenylsulfonyl)allyl)pyrrolidine-1-carboxylate (138), one step procedure.

To (-)-sparteine (3.60 mL, 15.0 mmol, 1.5 equiv) and N-Boc-pyrrolidine **134** (1.70 mL, 10.0 mmol) in 40 mL of diethyl ether at – 78 °C was added slowly a 1.4 M hexane solution of *s*-butyllithium (8.60 mL, 12.0 mmol). The reaction mixture was stirred for 5 h at – 78 °C and then a 0.5 M THF solution of $ZnCl_2$ (24.0 mL, 12.0 mmol) was added. The reaction was stirred for 1 h at this temperature and then CuBr•SMe_2 (~5 mol %, 0.15 g) was added in one portion followed by the addition of 2.20 g (10.0 mmol) of (*E*)-(3-chloro-1-propenylsulfonyl)benzene **139**. The resulting solution was allowed to warm slowly to room temperate overnight. The reaction mixture was poured into 200 mL of 5% phosphoric acid and an insoluble precipitate was removed by filtration through a celite pad. The product was extracted with diethyl ether. The extract was washed with an aqueous solution of K_2CO_3, dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (20% EtOAc/hexane) to afford 1.7 g (48% yield) of (*R*)-*tert*-butyl-2-(1-(phenylsulfonyl)allyl)pyrrolidine-1-carboxylate (**138**) as a 1:1 mixture of two diastereomers. The ^{1}H NMR ($CDCl_3$) and ^{13}C NMR ($CDCl_3$) spectra of (*R*)-*tert*-butyl-2-(1-(phenylsulfonyl)allyl)pyrrolidine-1-carboxylate (**138**) are given above.

(*E*)-(3-Chloro-1-propenylsulfonyl)benzene (139).

A 250 mL three-neck round-bottom flask was purged with argon and charged with 180 mL of dry dichloromethane and 3-chloroperoxibenzoic acid (11.2 g, 50 mmol). The flask was cooled to 0 °C and then 1-phenylthio-3-chloropropene **36** (4.0 g, 22 mmol) was added slowly. The reaction was stirred at 0 °C for 16 h and then the reaction was quenched with 200 mL of saturated water solution of K_2CO_3. The product was extracted with dichloromethane and then washed with brine. The extract was dried over $MgSO_4$ and concentrated in vacuo to give 4.6 g (ca. 100%) of the titled product **139**, which was used without further purification. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.88 (d, 2 H, J = 14.0 Hz), 7.61 – 7.50 (m, 3 H), 7.04 (dt, 1 H, J_1 = 14.8 Hz, J_2 = 5.3 Hz), 6.72 (d, 1 H, J = 14.8 Hz), 4.21 (d, 2 H, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$), δ (ppm): 139.8, 139.1, 133.3, 132.6, 129.0, 127.2, 41.1; exact mass calcd. for $C_9H_9O_2SCl$ 216.0012, found 216.0010.

(*R*)-1-Allyl-2-(1-(phenylsulfonyl)allyl)pyrrolidine (141).

A 100 mL one-neck round-bottom flask, equipped with gas inlet and magnetic stirrer, was purged with argon gas and charged with (*R*)-*tert*-butyl-2-(1-(phenylsulfonyl)allyl)-pyrrolidine-1-carboxylate (**138**) (3.40 g, 9.7 mmol) and 20 mL of dry dichloromethane. Trifluoroacetic acid (4.80 mL) was added dropwise to the solution at 0 °C and the resulting mixture was stirred at room temperature for 3 h. Then the reaction mixture was poured on ice (200 g) and treated with K_2CO_3 until the mixture registered a pH between 8 and 9. The product was extracted with dichloromethane. The extract was dried over $MgSO_4$ and concentrated in vacuo to yield (*R*)-2-(1-(phenylsulfonyl)allyl)pyrrolidine (**140**) in quantitative yield (2.30 g). The product **140** was found to be extremely sensitive to ambient atmosphere and was used immediately in the next stage.

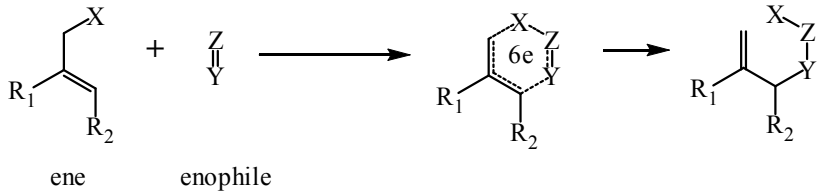
A 100 mL three-neck round-bottom flask, equipped with gas inlet, rubber septum and glass stopper, was purged with argon gas and charged with 2.30 g (9.2 mmol) of (*R*)-2-(1-(phenylsulfonyl)allyl)pyrrolidine (**140**), 50 mL of acetonitrile and K_2CO_3 (7.0 g, 50 mmol). Allyl bromide (1.6 g, 13 mmol) was added slowly at room temperature and the resulting mixture was stirred at this temperature for 2 days. Then the mixture was poured into 200 mL of water and extracted with dichloromethane. The combined organic extract was washed with a brine solution and dried over $MgSO_4$. The extract was concentrated in vacuo and was passed through a short silica gel column. The product was eluted with 20% EtOAc in hexane to afford 2.4 g (88%) of (*R*)-1-allyl-2-(1-(phenylsulfonyl)allyl)pyrrolidine (**141)** as a 1:1 mixture of two diastereomers. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.80 (d, 2 H, J = 7.8 Hz), 7.59 – 7.46 (m, 3 H), 6.00 (ddd, 1 H, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 9.9 Hz), 5.89 – 5.76 (m, 1 H), 5.22 – 5.12 (m, 2 H), 5.05 (d, 1 H, J = 9.9 Hz), 4.77 (d, 1 H, J = 17.1 Hz), 3.73 – 3.63 (m, 2 H), 3.40 (dd, 1 H, J_1 = 9.9 Hz, J_2 = 3.0 Hz), 3.08 – 2.96 (m, 2 H), 2.45 – 2.37 (m, 1 H), 2.10 – 2.06 (m, 1 H), 1.76 – 1.64 (m, 3 H); exact mass calcd. for $C_{16}H_{22}NO_2S$ 292.1371, found 292.1369.

4.0 ZINC-ENE CYCLIZATIONS. A NOVEL ITERATIVE APPROACH TO DI- AND TRIQUINANE SYNTHESES

4.1 INTRODUCTION

4.1.1 "Ene"-reactions.

The "ene" reaction is the addition of a compound with a double bond having an allylic hydrogen (the "ene") to a compound with a multiple bond (the "enophile"), as shown in Scheme 4.1.[158,159] When X = H, it is the regular "ene"-reaction. A high temperature or the presence of Lewis acids is required for such a reaction. When X = Li, Mg, Zn, B, Al, Pd, Pt or Ni, they are known as metallo-ene reactions. The advantage of metallo-ene reactions is that the reaction conditions are relatively less demanding than the corresponding thermal ene-reactions. Moreover, much more functionality can be introduced simply by trapping the formed organometallics with various electrophiles (for M = Li, Mg and Zn).[160,161] The best known Pd-ene reaction is the polymerization of butadiene.[162]



X = H - regular "ene"-reaction. X = M - metallo-ene reaction

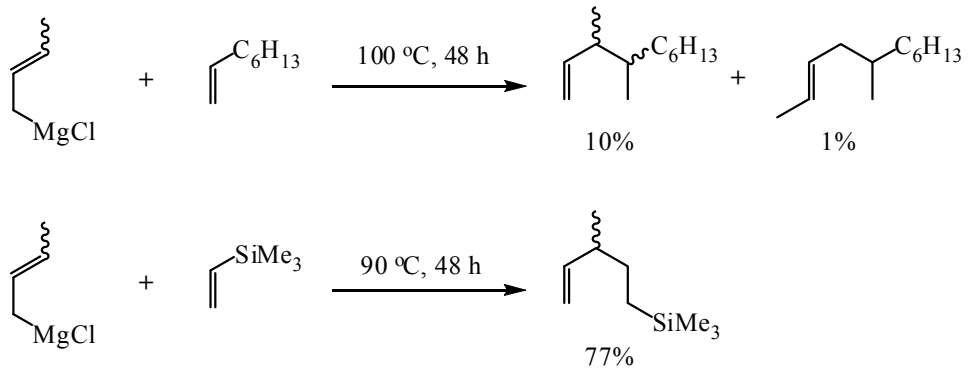
enophile = carbonyl and thiocarbonyl compounds, imines, alkenes, alkynes

Scheme 4.1. "Ene"-reactions.

4.1.1.1 Intermolecular Metallo-ene Reactions

4.1.1.1.1 Intermolecular Magnesium-ene Reactions.

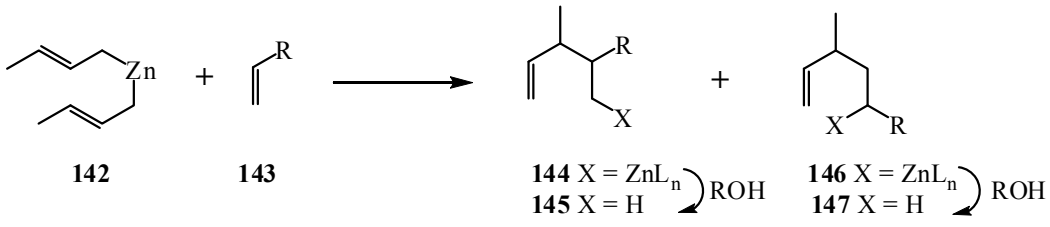
As illustrated in Scheme 4.2, the addition of allylmagnesium chloride to a non-strained alkene, 1-octene, is inefficient. The products are obtained in low yield and poor regio- and diastereoselectivity.[160] However, the addition of allylmagnesium chloride to a TMS substituted olefin gave synthetically useful regioselectivity and yield.[158]



Scheme 4.2. Intermolecular addition of allylmagnesium chloride to olefins.

4.1.1.1.2 Intermolecular Zinc-ene Reactions.

Preformed dicrotylzinc **142** underwent zinc-ene reactions with terminal alkenes under very mild conditions (20–50 °C) to give, after protonolysis, the alkene **145** (Scheme 4.3, Table 4.1).[161] For simple unconjugated alkenes, the reactions are clean and almost pure regioisomers are obtained in good yields (Table 4.1, entry 1 and 2). However, the reaction has poor regioselectivity for conjugated olefins like butadiene and styrene (Table 4.1, entry 3 and 4). In general, the diastereoselectivity of **145** is low for all cases.

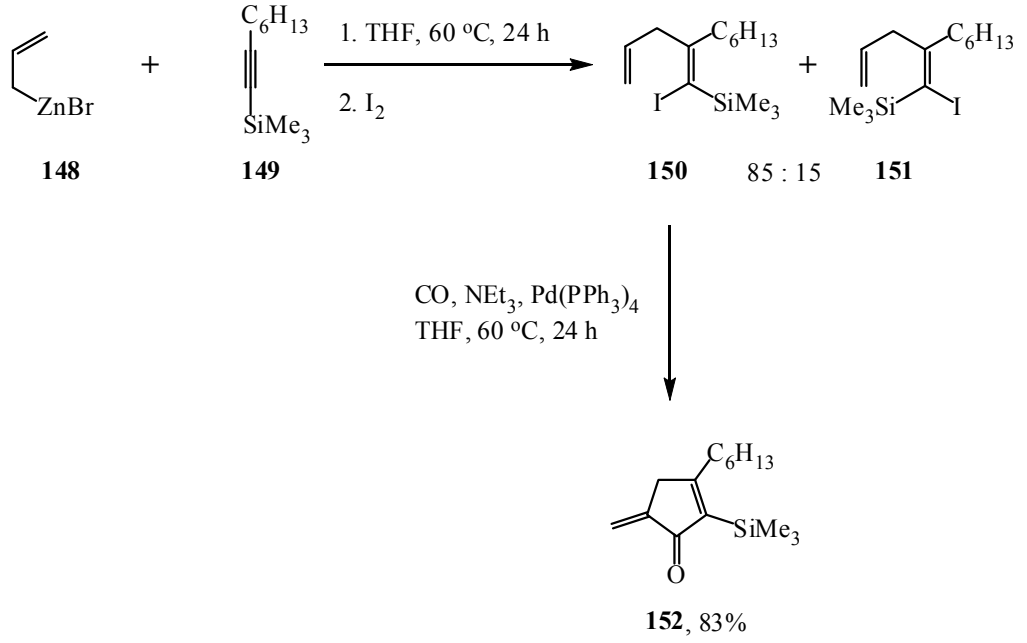


Scheme 4.3. Intermolecular Zn-ene reactions.

Table 4.1. Intermolecular Zn-ene reaction: product and diastereomeric ratios

Entry	*R*	*Temperature and time*	*Yield 145 +147*	*Ratio 145/147*	*Diastereomeric ratio of 145*
1	C_6H_{13}	50 °C, 20 h	85	100 : 0	35 : 65
2	Ph	20 °C, 66 h	42	33 : 67	75 : 25
3	$CH{=}CH_2$	20 °C, 43 h	81	42 : 58	52 : 48

As shown in Scheme 4.4, the trimethylsilyl group is able to control completely the regioselectivity of the intermolecular addition of an allylzinc bromide **148** to a silylated alkyne **149** and the 1,1-dimetalloalkene intermediate can be iodinated to afford compounds **150** and **151**, respectively, with a ratio of 85:15.[163] Vinyl iodide **150** can undergo Pd-catalyzed carbon monoxide insertion to afford α,β-unsaturated cyclopentenone **152**.



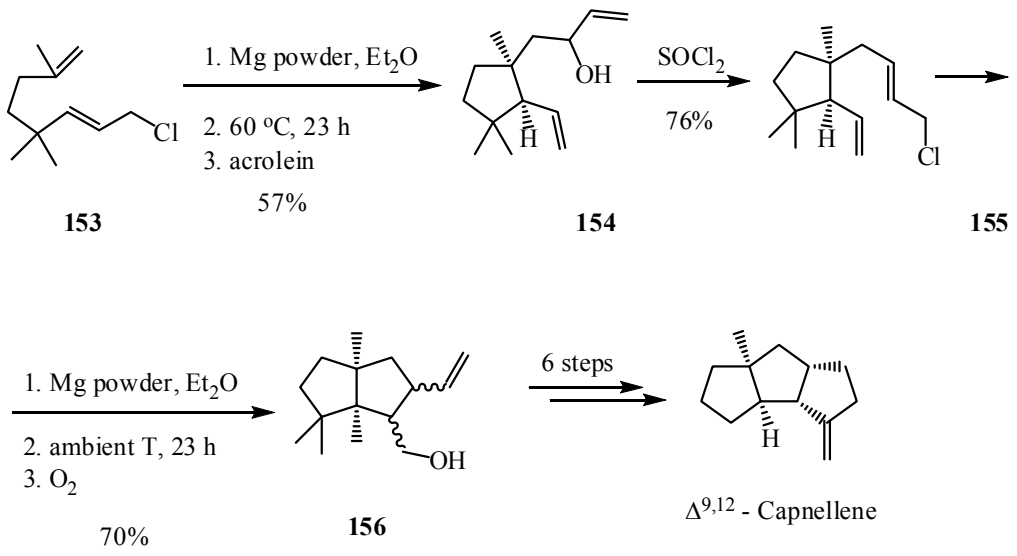
Scheme 4.4. Novel synthesis of α,β-unsaturated cyclopentenone via allylzincation of an alkyne.

4.1.1.2 Intramolecular Metallo-ene Cyclizations.

In contrast to intermolecular metallo-ene reactions, the intramolecular versions are more entropically favored and should be more regio- and stereo-selective due to the rigid transition state for the ring formation.

4.1.1.2.1 Intramolecular Magnesium-ene Cyclizations.

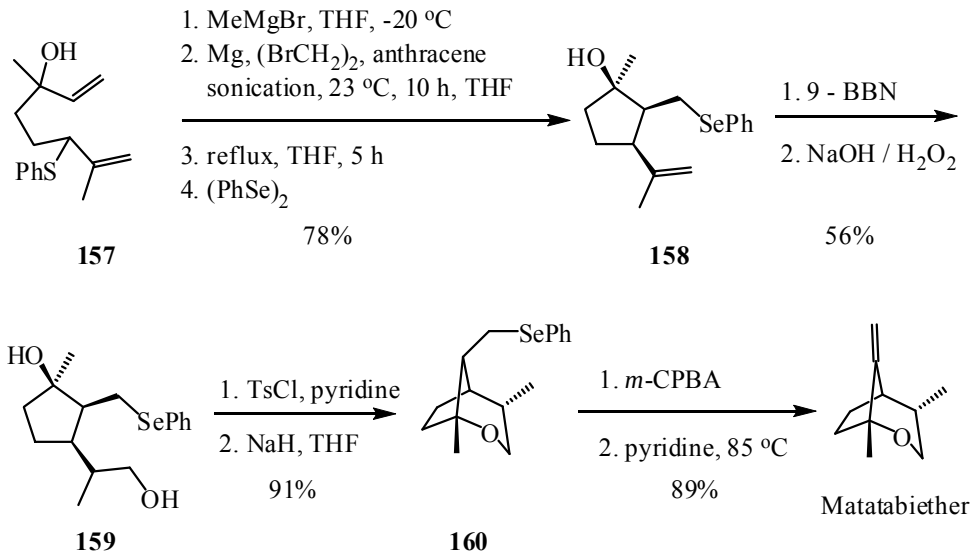
Intramolecular magnesium-ene reactions are well known for the syntheses of 5-membered rings in a stereoselective fashion due to the work of many chemists, especially Oppolzer.[158,159] Scheme 4.5 shows the total synthesis of $\Delta^{9,12}$–capnellene by using two magnesium-ene cyclizations as the key steps to construct two cyclopentane rings.[164] Treatment of allylic chloride **153** with magnesium powder afforded the corresponding allylmagnesium chloride which underwent the intramolecular magnesium-ene cyclization to provide a cyclopentane ring with high stereoselectivity. After the cyclization product was treated with acrolein, compound **154,** was obtained. Treatment of allylic alcohol **154** with $SOCl_2$ provided the corresponding allylic chloride **155**. The second magnesium-ene cyclization gave, after trapping the product with oxygen, the alcohol **156**, which was further elaborated in six steps to $\Delta^{9,12}$–capnellene.



Scheme 4.5. Two magnesium-ene cyclizations as key steps in the total synthesis of $\Delta^{9,12}$–capnellene.

Many other superb total syntheses of natural products have been created based on this methodology. For instance, the syntheses of (±)-6-protoilludene,[165] sinularene,[166] 12-acetoxysinularene,[167] (+)-α-skytanthine,[168] all involve highly diastereoselective magnesium-ene cyclizations as the key steps.

Recently, Cohen and co-workers developed a novel method to perform the magnesium-ene cyclization by using allyl phenyl sulfides as precursors of the allylmagnesium species.[169] As illustrated in Scheme 4.6, compound **157** was first treated with MeMgBr to deprotonate the allylic OH-group followed by reductive allyl magnesiation using the magnesium-anthracene-THF complex. The magnesium-ene cyclization proceeded smoothly. After the cyclization product was treated with $(PhSe)_2$, compound **158** was obtained with high stereoselectivity. Further elaboration completed the most efficient synthesis to date of racemic matatabiether.



Scheme 4.6. Synthesis of metatabiether using the Mg-ene cyclization as the key step.

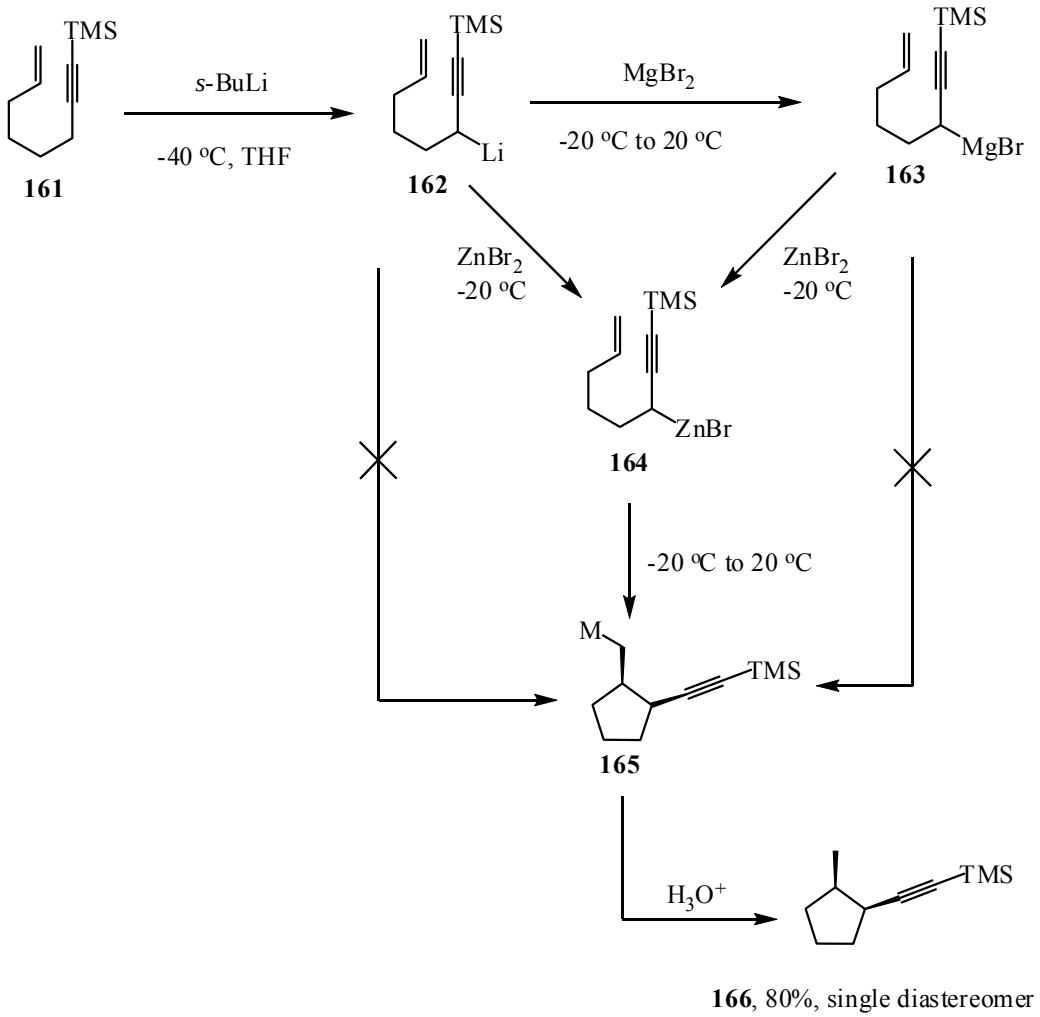
Allyl phenylsulfides will probably prove to be superior to allyl halides as precursors of allylmagnesium species due to their ease of assembly, particularly in a connective fashion, and also because allyl phenyl sulfides, unlike allyl halides, give no coupling product upon treatment with magnesium.

One major limitation of the intramolecular Mg-ene reaction is that olefinic enophiles can only be terminally unsubstituted or strained olefins.[158] Another limitation is that attempts to apply these cyclizations to the preparation of pyrrolidines have so far failed.[158]

4.1.1.2.2 Intramolecular Zinc-ene Cyclizations.

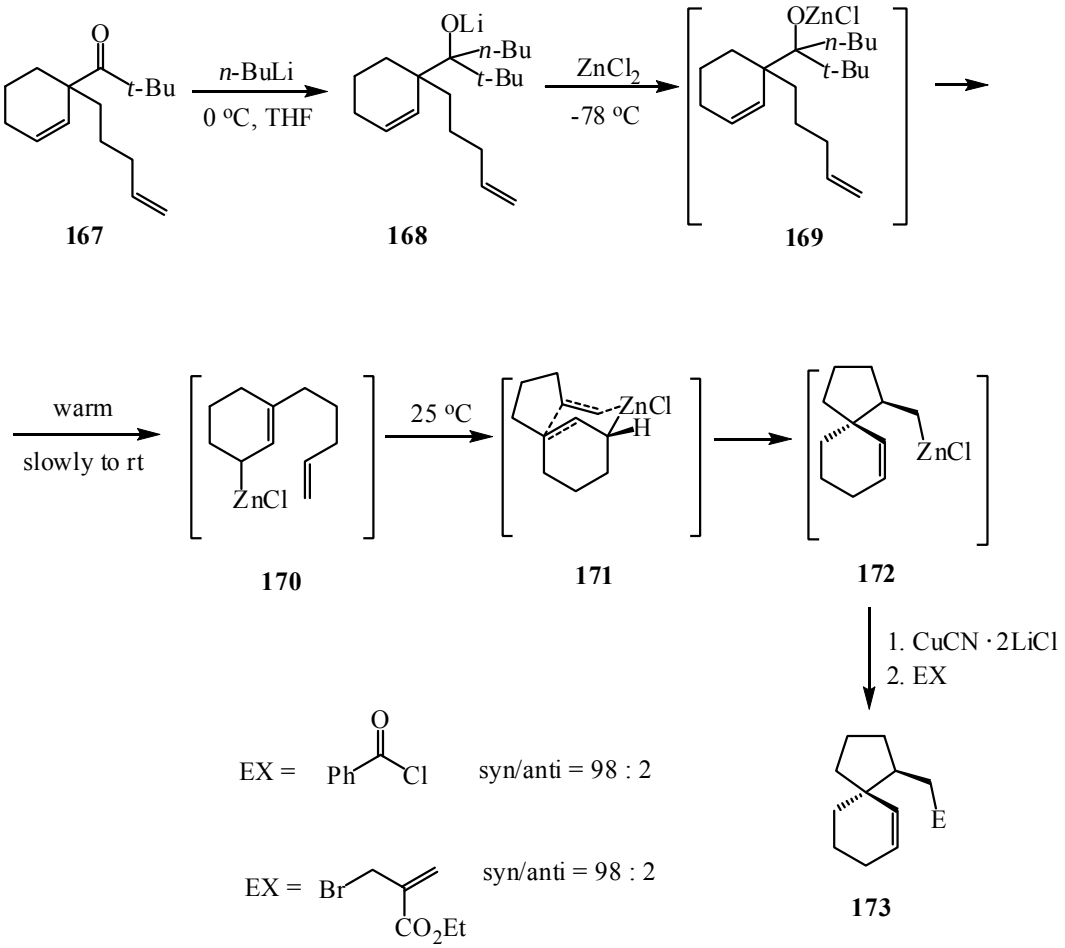
Due to unreactive nature of organozinc species, intramolecular "zinc-ene" cyclizations have the potential to combine high stereochemical control over the cyclization, the possibility of trapping the cyclized intermediates with various electrophiles and compatibility with various

functionalities. However, intramolecular zinc-ene reactions have not been widely used in organic synthesis. This is almost certainly due to the tedious preparation method required for the generation of allylzincs. Traditionally, allylzincs are obtained by means of transmetallation of allyllithiums. As shown in Scheme 4.7, a propargyllithium **162**, produced by treating alkyne **161** with *sec*-BuLi, does not undergo the lithium-ene cyclization under the reaction conditions.[170] The corresponding propargylmagnesium **163**, prepared by transmetallation of **162**, does not undergo the magnesium-ene cyclization either.[170] However, treating **162** or **163** with $ZnBr_2$ at -20 °C leads to the generation of a propargylzinc **164**, which undergoes smooth zinc-ene cyclization to afford the cyclized intermediate **165**. The product **166** is formed from **165** with excellent yield and stereoselectivity after protonolysis.[170]



Scheme 4.7. Zinc-ene cyclization by transmetallation from propargyllithium and propargylmagnesium bromide

Knochel reported an alternative approach to allylzinc reagents followed by zinc-ene cyclization to construct spirobicyclic molecules,[171] as depicted in Scheme 4.8.

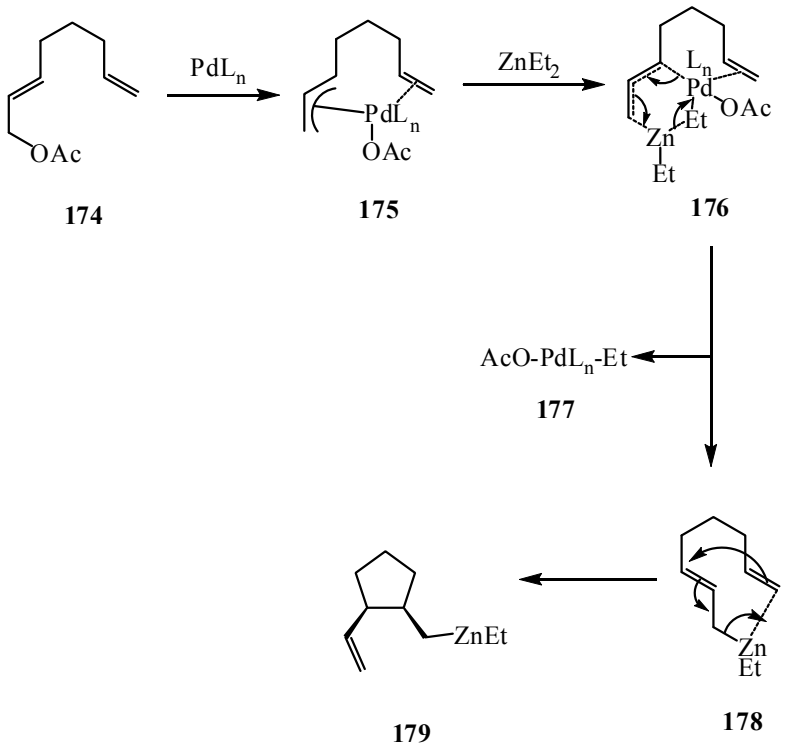


Scheme 4.8. Knochel's allylzinc generation followed by the zinc-ene cyclization.

The tertiary homoallylic lithium alcoholate **168**, generated by treating the ketone **167** with *n*-BuLi, is treated with $ZnCl_2$ to form the corresponding zinc alcoholate **169**, which fragments to afford the allylzinc **170**. The intermediate product **170** cyclizes efficiently at room temperature through transition state **171** to furnish a spirobicyclic intermediate **172** in a highly stereoselective fashion. The resulting alkylzinc **172** undergoes transmetallation with CuCN•2LiCl to afford the corresponding cuprate which could be quenched with an appropriate electrophile to produce **173**.[171] Unfortunately, neither Knochel nor anybody else has ever

reported the use of this reaction in synthesis. Moreover, the published paper [171] does not contain any detailed reaction conditions or any other examples.

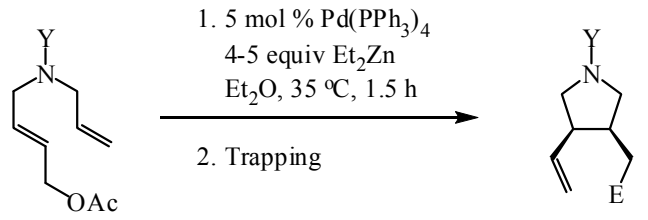
In 1994, using allyl acetates as the substrates, Oppolzer developed the Pd-catalyzed zinc-ene cyclization method[172] to overcome the poor functional group tolerance due to the nature of allyllithium and allylmagnesium intermediates used in transmetallation reactions. As shown in Scheme 4.9, the mechanism of this reaction is thought to involve Pd^0 insertion into allyl acetate **174** to generate the π-allylpalladium intermediate **175** that can undergo transmetallation with dialkylzinc through the transition state **176** to give the corresponding allylzinc intermediate **178,** together with ethylpalladium acetate **177**. The allylic zinc can attack the carbon-carbon multiple bond efficiently to give cyclized organozinc **179** which can be trapped by an electrophile to form a final product. Ethylpalladium acetate **177** undergoes β-hydride elimination to release ethylene and to regenerate Pd^0. Then the regenerated Pd^0 can participate in the catalytic cycle again.[172] Since the release of ethylene is the key to drive the reaction in the forward direction, the use of dimethylzinc, Me_2Zn, instead of Et_2Zn causes no reaction because the methyl group has no β-hydride available for the elimination.[172]



174 **175** **176** **177** **178** **179**

Scheme 4.9. Proposed mechanism of the palladium catalyzed intramolecular zinc-ene reaction.

By utilizing this method, 2,3-disubstituted pyrrolidine derivatives, which are not available by the magnesium-ene cyclization (probably due to the facile elimination of allyl amines from the allylmagnesium intermediate before the cyclization), have been synthesized with high diasterioselectivity by intramolecular addition of an allylzinc to an olefin (Scheme 4.10).[172]

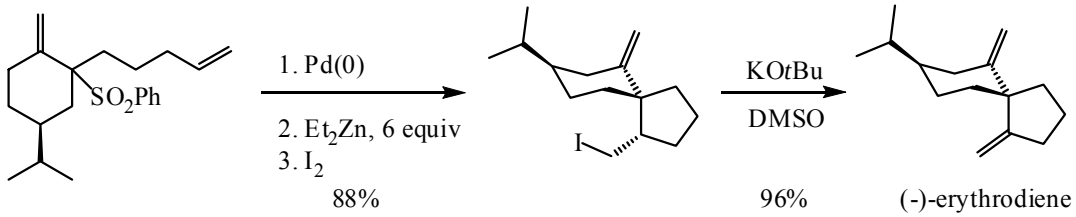


180 **181**

Y = CPh_3,	E = H	cis/trans = 92 : 2	79%
Y = Tosyl	E = H	cis/trans = 96 : 4	44%
Y = Tosyl	E = I	cis/trans = 96 : 4	51%

Scheme 4.10. Synthesis of pyrrolidine derivatives by intramolecular addition of allylzincs to alkenes.

Recently, Cohen and co-workers published a total synthesis of the natural sesquiterpene (-)-erythrodiene, using an allyl phenyl sulfone as the precursor for the Pd-catalyzed zinc-ene cyclization as a key step instead of exploiting allyl acetates (Scheme 4.11).[173] Multiple advantages of using allyl sulfones in place of allyl acetates as precursors to allylzincs were cited.[173]



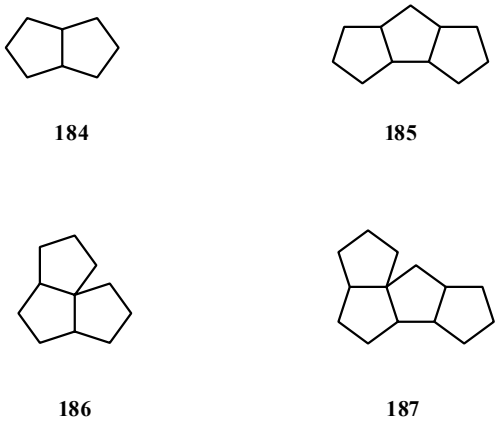
182 **183**

Scheme 4.11. An allyl phenyl sulfone as a key intermediate for the Pd-catalyzed zinc-ene cyclization in the total synthesis of (-)-erythrodiene

We envisioned that the use of allyl phenyl sulfides as precursors for zinc-ene cyclization, upon treatment treated with LDMAN followed by transmetallation with $ZnCl_2$, could provide an excellent alternative to traditional allyl acetates and Pd-catalyzed zinc-ene cyclizations, due to the ease of preparing allyl phenyl sulfides, particularly by copper catalyzed organozinc γ-allylic substitution reactions. The efficiency of substrate preparation and substrate usage would be demonstrated by the formal syntheses of $\Delta^{9,12}$–capnellene and some other ring-fused triquinane-type products.

4.1.2 Polyquinanes

While polyquinanes have been in nature since time immemorial, they were discovered only recently. For example, the structure determination of one of the "authentic" polyquinane natural products, $\Delta^{9,12}$–capnellene, was accomplished only in 1978.[174] Despite this, the discovery of polyquinane natural products has rapidly proliferated and they have been encountered among plant, marine, and microbial sources. Polyquinane skeletons have been found among sesqui-, di-, sesterterpenes and even in steroids. So far, natural products containing up to four fused five-membered rings have been discovered. Structures **184 - 187** represent the characteristic polyquinane frameworks (Scheme 4.12).

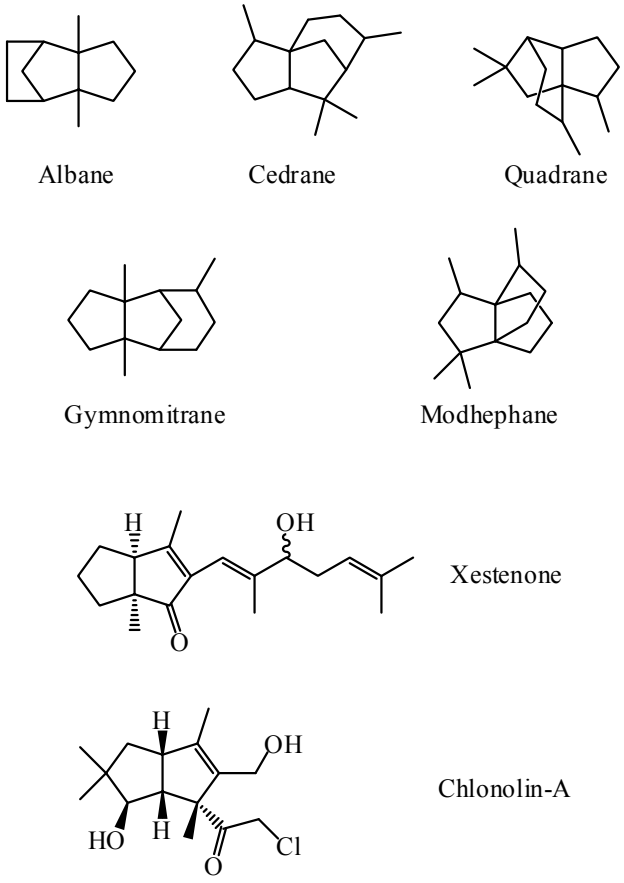


Scheme 4.12. Characteristic polyquinane carbocyclic skeletons.

The polyquinane natural products, quite expectedly, have aroused a great deal of interest among synthetic chemists in recent years, primarily on account of the architecturally pleasing assembly of five-membered rings, embellished with a number of methyl groups and the wide-ranging biological activity exhibited by some members of this family.[175] Indeed, polyquinanes have provided a large new field for the development of new strategies for cyclopentannulations. In view of this intense activity directed toward polyquinane synthesis, the literature on the subject has been periodically reviewed, particularly by Paquette.[176,177,178]

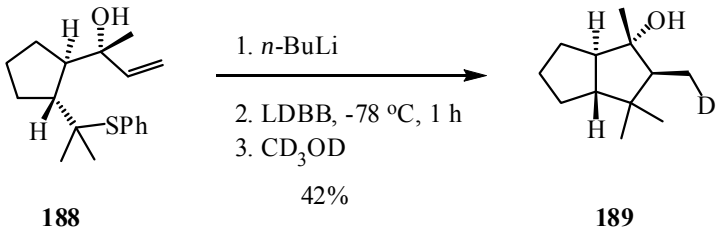
4.1.2.1 Diquinanes

The occurrence of the diquinane moiety as a part of a structure among terpenes has been known for a long time (*e.g.* albane, cedrane, gymnomitrane), but the isolation of products composed solely of the diquinane unit, such as xestenone and chlonolin, is more recent (Scheme 4.13).[175]



Scheme 4.13. Examples of the natural products exhibiting diquinane moiety.

Over the years, these ring systems have attracted considerable interest among synthetic chemists. Cohen and co-workers have recently been successful in obtaining the diquinane skeleton through the use of the intramolecular addition of an alkyllithium, formed by reductive lithiation, to an alkene and the accelerating affect of an oxyanionic group on this cyclization (Scheme 4.14).[179]



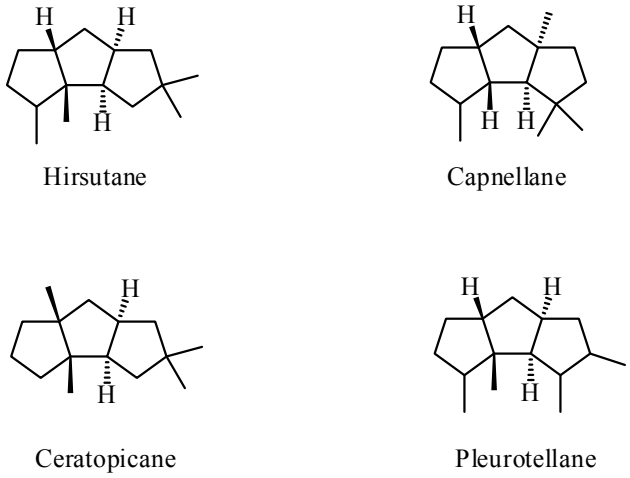
188 **189**

Scheme 4.14. Formation of the *trans*-fused diquinane system.

Due to strain at the fused ring junction, a *trans*-fused diquinane is approximately 4 kcal/mol higher in energy than its *cis* relative, making the *trans* skeleton a more impressive goal to reach.[180] However, due to the facilitating effect of the allylic oxyanionic group and favorable thermodynamics, a relatively inaccessible *trans*-bicyclo[3.3.0]octane can be prepared.

4.1.2.2 Linear Triquinanes

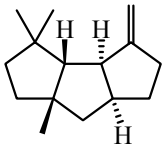
Among the natural products bearing a linear triquinane framework isolated so far, only the thermodynamically favored *cis,anti,cis*-ring fusion has been encountered. There are four different skeletal types known among the linear triquinane natural products (Scheme 4.15), representing variation in the location of the four carbon substituents and quaternary carbon centers. However, they all share a common biosynthetic origin through the humulene cyclization cascade.



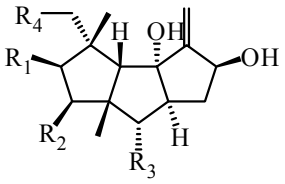
Scheme 4.15. Four different skeletal types known among the linear triquinane natural products.

The main challenge in the synthesis of linear triquinane natural products has been the rapid construction of five-membered rings for which a number of new very different cyclopentannulation protocols have been developed. The control of ring junction stereochemistry in these natural products has never been a serious problem as the *cis,anti,cis*-stereochemistry is overwhelmingly preferred.

Capnellene **190** (Scheme 4.16), the simplest member of the capnellane group of marine sesquiterpenes, was isolated by Djerassi *et al.* in 1978 from the soft coral *Capnella imbricata*.[181] Earlier, several oxygenated capnellanes **191-196** (Fig 4.16) were also isolated from the same source.[182]



Capnellene (**190**)

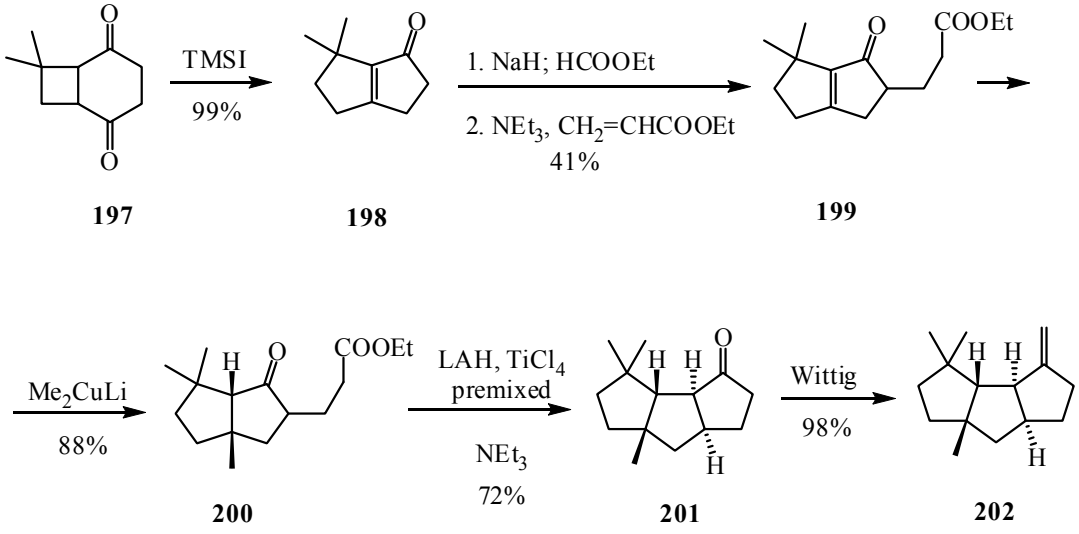


191, $R_1=R_2=R_3=R_4=H$
192, $R_1=R_3=R_4=H$; $R_2=OH$
193, $R_1=R_2=R_4=H$; $R_3=OH$
194, $R_2=R_3=R_4=H$; $R_1=OH$
195, $R_1=R_3=H$; $R_2=R_4=OH$
196, $R_2=R_4=H$; $R_1=R_3=OH$

Scheme 4.16. Isolated capnellanes.

A combination of interesting structural features and potential biological activity has sustained the interest of synthetic chemists in this class of sesquiterpenoids.[183]

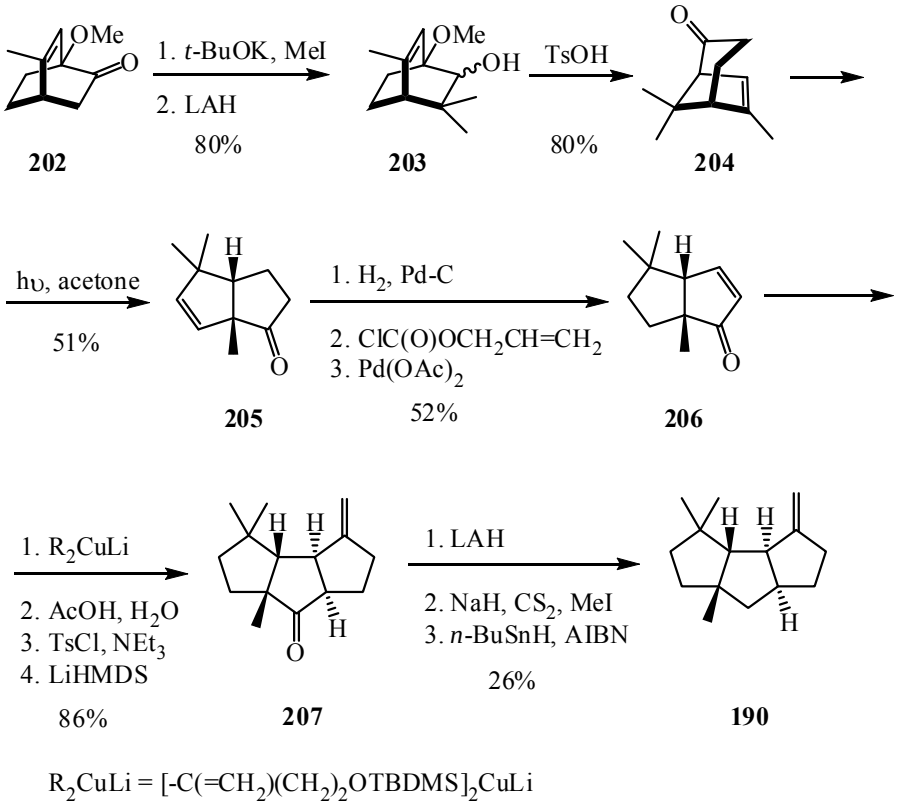
Oda and co-workers have reported the synthesis of (±)-capnellene **190** exploiting an intramolecular Ti(0)-mediated ester-ketone reductive coupling as the key reaction from **200** to **201** (Scheme 4. 17).[184]



Scheme 4.17. Oda's (±)-capnellene synthesis.

The diquinane enone **198** was obtained by the trimethylsilyl iodide-mediated rearrangement of the bicyclo[4.2.0]octane-2,5-dione **197**. Introduction of the ethyl acrylate side chain and conjugate addition of the methyl group to enone **199** led to the keto ester **200** which upon titanium coupling furnished the precursor **201** of (±)-capnellene **190**.

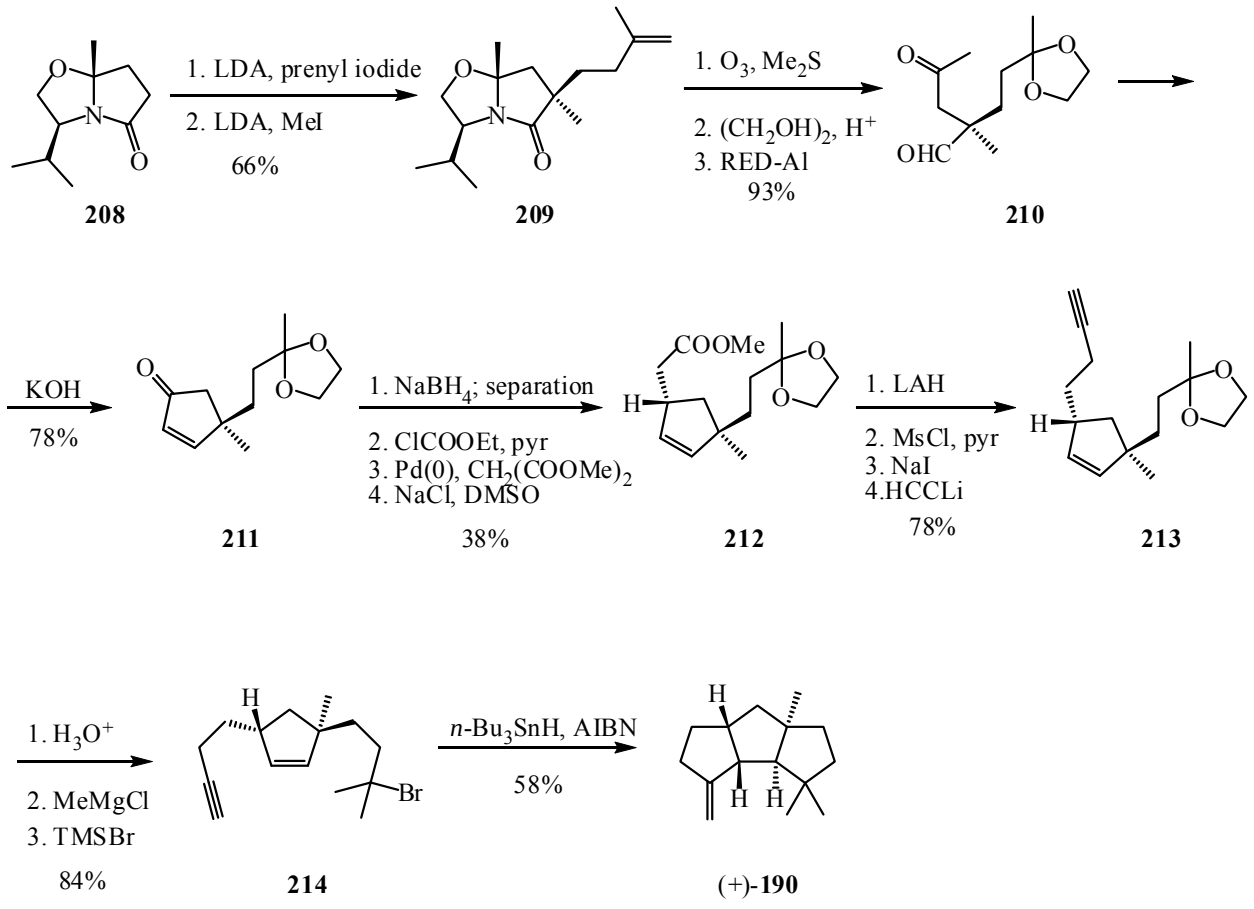
Uyehara and co-workers have explored the photochemical 1,3-acyl shift in a bicyclo[3.2.1]oct-6-en-2-one derivative **204** for generating the diquinane unit **205** of capnellene **190** (Fig 4.18).[185]



Scheme 4.18. Uyehara's (±)-capnellene synthesis.

The requisite bicyclo[3.2.1]octane precursor **204** was obtained through a regioselective rearrangement of bicyclo[2.2.2]oct-5-en-2-ol derivative **203**. The third cyclopentane ring was annulated via the conjugate addition of a functionalized vinyl cuprate and intramolecular alkylation to give the triquinane **207**. Deoxygenation of **207** completed the synthesis of (±)-capnellene **190**.

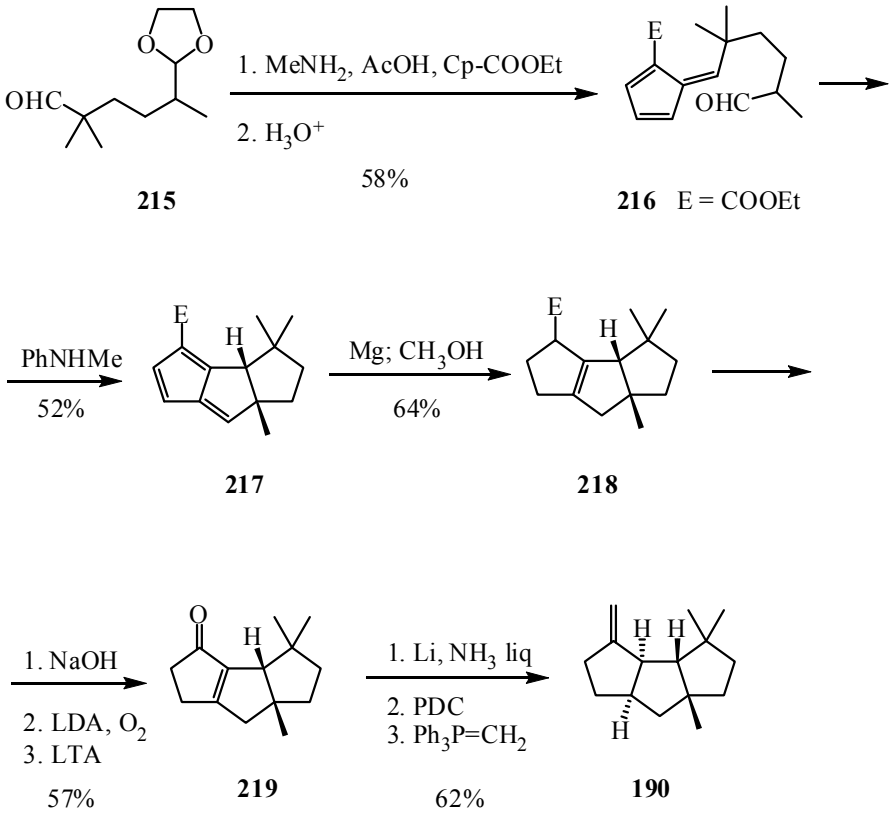
Meyers and Bienz[186] exploited the sequential alkylation on their chiral auxiliary, the bicyclic lactam **208**, to furnish, after further manipulations, **210** leading to an enantioselective synthesis of the unnatural capnellene antipode (+)-**190** (Scheme 4.19).



Scheme 4.19. Meyers' unnatural (+)-capnellene synthesis.

A series of functional group modifications in **211** led to Curran's intermediate[187] **214**. Tandem radical cyclizations in the bromo enyne **214** resulted in (+)-capnellene **190**.

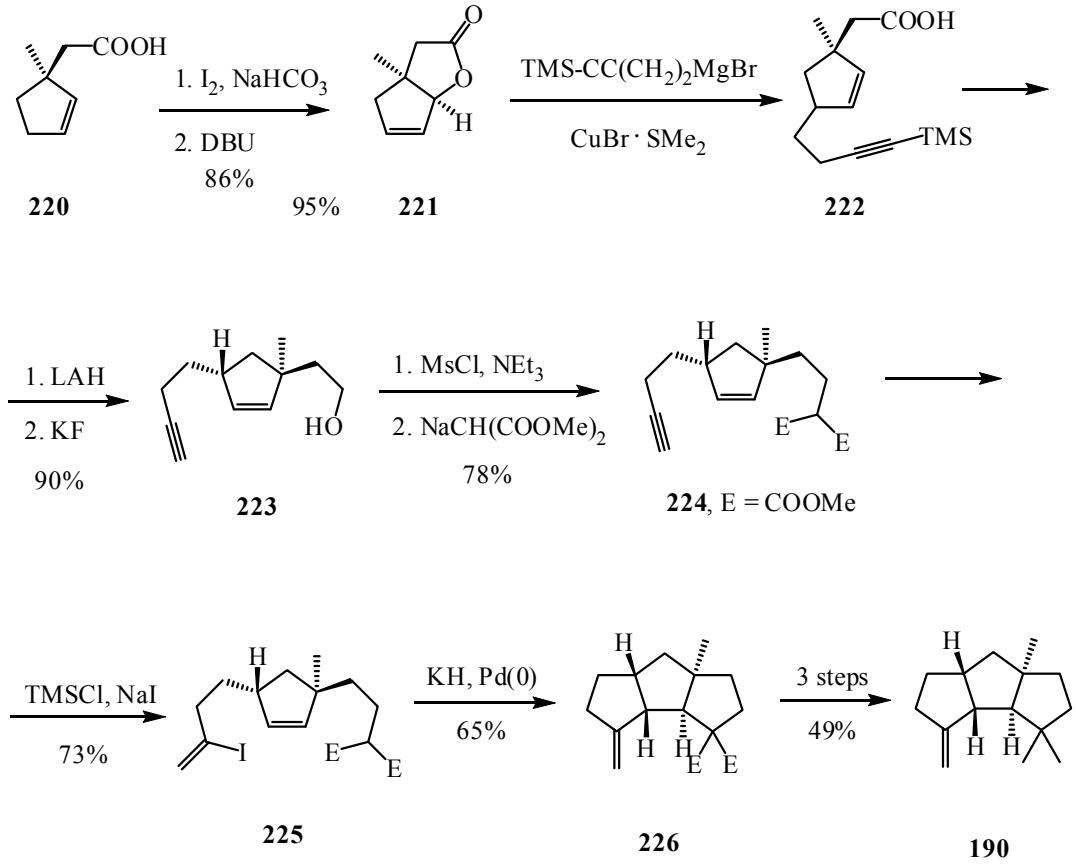
A higher order intramolecular [6+2]-cycloaddition between fulvene and an aldehyde was the main strategy (**216** to **217**) employed by Houk and coworkers for the rapid construction of the triquinanes framework present in (±)-capnellene **190** (Fig 4.20).[188]



Scheme 4.20. Houk's (±)-capnellene synthesis.

Partial and regioselective reduction within the fulvene system **217** and further functional group manipulations led to the desired natural product.

A palladium-catalyzed tandem cyclization strategy was employed for the synthesis of (±)-capnellene **190** by Balme and Bouyssi (Scheme 4.21).[189]

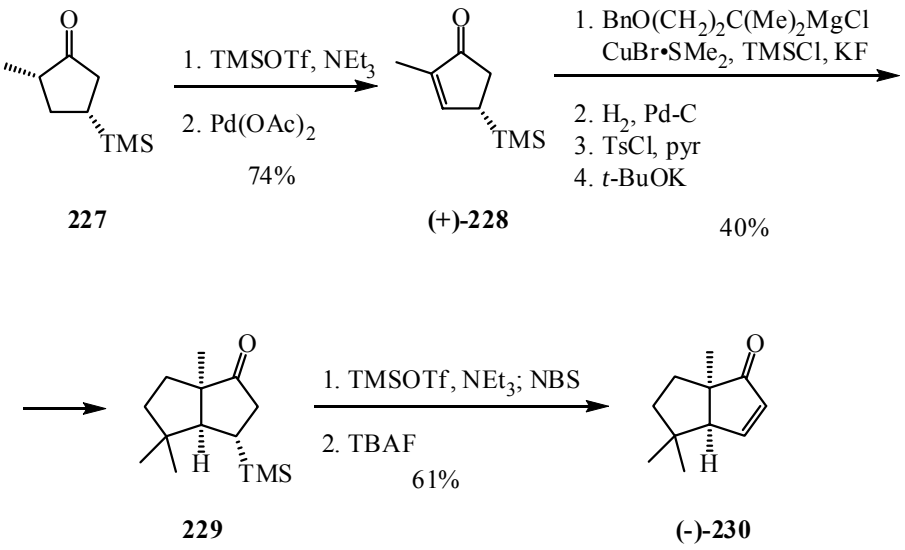


Scheme 4.21. A palladium-catalyzed tandem cyclization strategy in (±)-capnellene synthesis.

The malonate **224**, obtained from the lactone **221**, was transformed into the vinyl iodide **225**. Palladium mediated cyclization of **225** furnished the triquinanes **226**, and the ester groups were transformed to a *gem*-dimethyl group to result in (±)-capnellene **190**.

Asaoka and co-workers have reported an enantioselective synthesis of a chiral enone (-)-**230** (Scheme 4.22), which is a non-racemic version of diquinane **206** (Scheme 4.18).[190] Silyl

group-directed conjugate addition to the cyclopentenone (+)-**228** and functional group manipulations led to (-)-**230**. This product can be further used in an enantioselective synthesis of (-)-capnellene **190** as, for example, it was done by Uyehara and co-workers.[185]



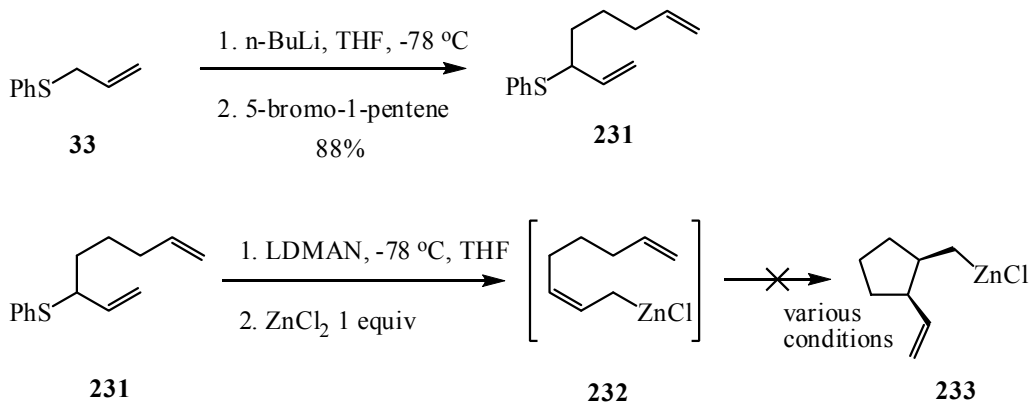
Scheme 4.22. Enantioselective synthesis of the chiral enone (-)-**230**.

As has already been mentioned in the current chapter, Oppolzer and co-workers developed a stereoselective synthesis of (±)-capnellene **190** exploiting intramolecular magnesium-ene reactions as depicted in Scheme 4.5.[164]

4.2 RESULTS AND DISCUSSION

Unfortunately, in our hands, the zinc-ene cyclization reported in 1999 by Knochel[171] (Scheme 4.8) was found to be non-reproducible and all attempts to observe any cyclized product

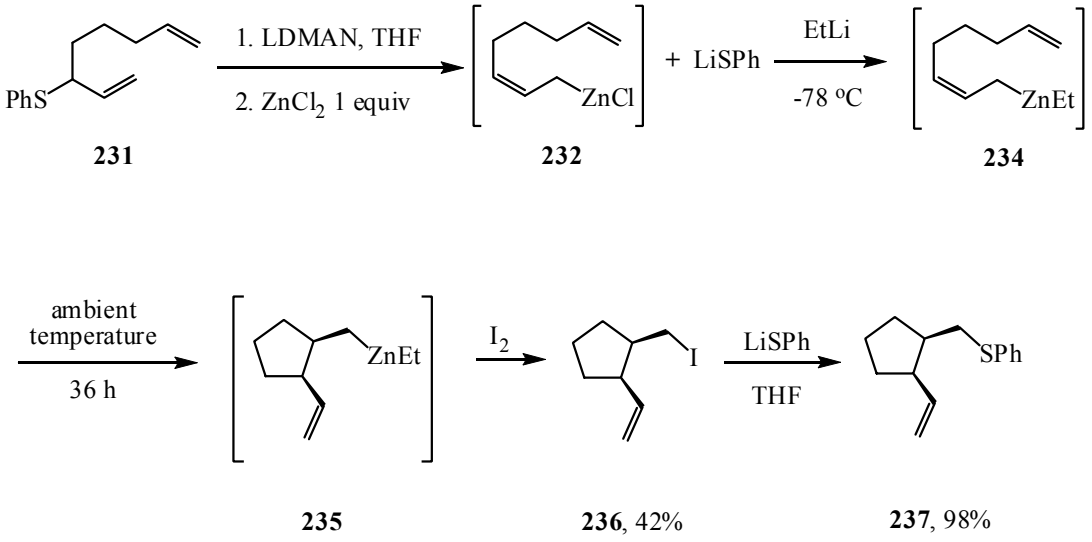
failed. In order to study the zinc-ene cyclization reaction thoroughly, 3-phenylthio-1,7-octadiene **231**, prepared by allylation of 5-bromo-1-pentene (Scheme 4.23), has been chosen as a precursor for the corresponding allylzinc compound **232**, the intended substrate for the intramolecular cyclization (Scheme 4.23). Reductive lithiation followed by transmetallation with 1 equiv of $ZnCl_2$ was used to convert **231** into the desired allylzinc chloride **232**, which was subjected to various conditions including stirring for 24 h either at ambient temperature or at reflux in THF (Scheme 4.23). All reactions were quenched with iodine. However, the cyclization product was never obtained, while a modest yield of 1-iodo-2,7-octadiene was observed.



Scheme 4.23. Zinc-ene cyclization reaction fails when allylzinc chloride is used as a substrate.

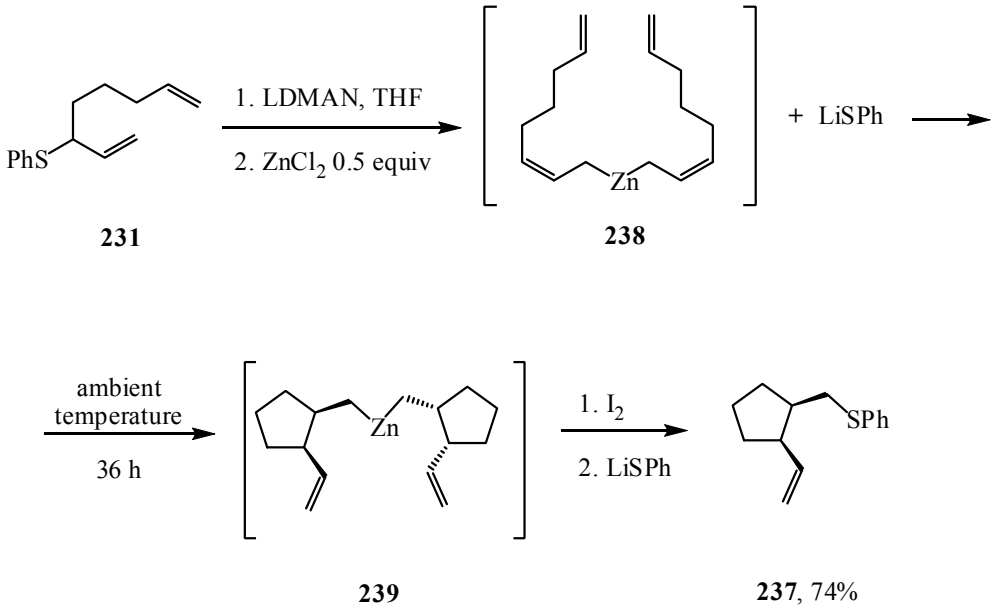
The only significant difference, besides the absence of a palladium-catalyst, between the intended zinc-ene cyclization depicted in Scheme 4.23 and the mechanism proposed by Oppolzer (Scheme 4.9)[172] and later exploited by Cohen and co-workers (Scheme 4.11)[173] is that the failed cyclization in Scheme 4.23 used an allylzinc substrate with only one organic ligand linked to the zinc atom. When the chlorine moiety in **232** was replaced with an ethyl group (Scheme 4.24), the cyclized product was observed at ambient temperature in 36 h. Unstable product **236** was

converted into *cis*-sulfide **237**, which was previously obtained and thoroughly studied along with *trans*-sulfide **237** by Shirong Zhu in this laboratory using a different synthetic method (Scheme 4.24).[191]



Scheme 4.24. Zinc-ene cyclization of allyl ethylzinc.

Even a better result was observed when a diallylzinc was utilized as a reagent in the zinc-ene cyclization (Scheme 4.25). In this case only a half equivalent of dry $ZnCl_2$ is required and no additional reagent, such as EtLi, was required.

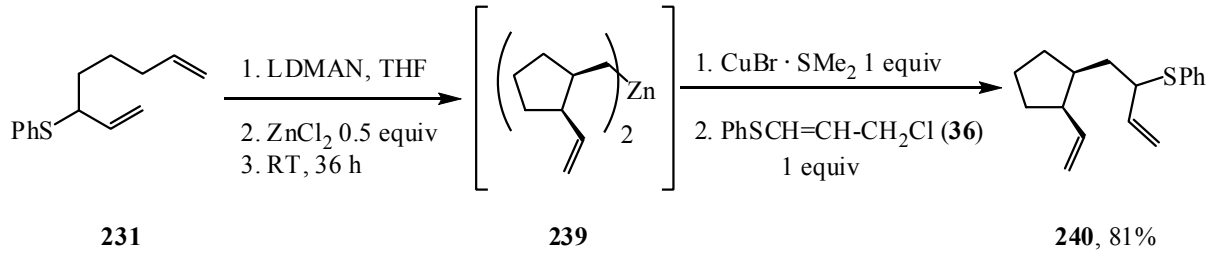


Scheme 4.25. Zinc-ene cyclization of a diallylzinc.

The c*is*-stereochemistry of the sulfide **237** was assigned based on ^{1}H-NMR since the *cis*- and *trans*- isomers have very different spectra.[191]

The considerably modest yield of the final sulfide **237** observed in syntheses depicted in Schemes 4.24 and 4.25 can be explained by the instability of the intermediate iodide product **236**, which must be separated from diphenyl disulfide formed during the iodine-quenching process by oxidation of LiSPh. Moreover, the yield of the desired iodide **236** can be diminished by the competitive reaction of **236** with LiSPh, which was generated in the reductive lithiation reaction and was not immediately oxidized by I_2.

An alternative and more sophisticated procedure was to submit the cyclized dialkylzinc **239** directly to the copper(I) catalyzed γ-allylic substitution reaction with 1-phenylthio-3-chloropropene **36** to produce the extremely versatile product **240** (Scheme 4.26), which can be used in a number of transformations, including further zinc-ene cyclization.

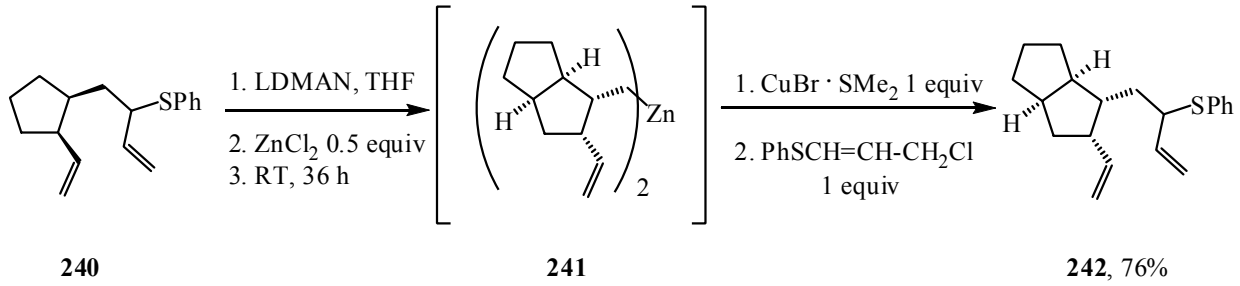


231 **239** **240**, 81%

Scheme 4.26. Zinc-ene cyclization of a diallylzinc in combination with a γ-allylic substitution reaction.

It is necessary to use a whole equivalent of CuBr•SMe_2 in order to convert the other strong nucleophile LiSPh, formed as a byproduct of the reductive lithiation, into the non-nucleophilic form of CuSPh. The latter is almost completely insoluble in THF and was used as a catalyst in the subsequent γ-allylic substitution reaction (Scheme 4.26). The c*is*-stereochemistry of the allylic sulfide **240** was assumed based on the c*is*-stereochemistry of the sulfide **237** (Scheme 4.25) observed in the same conditions.

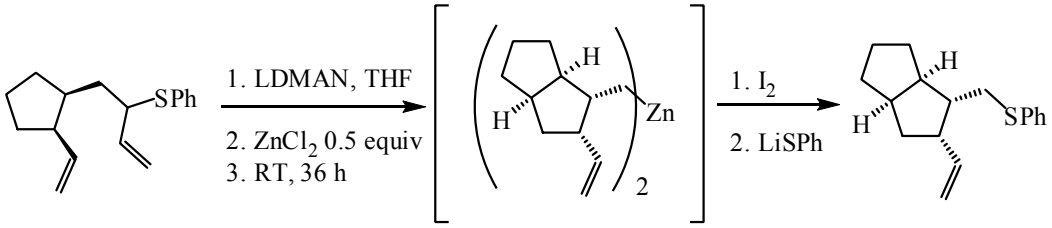
The product **240**, possessing the octadiene moiety analogous to that of the starting sulfide **231**, was subjected to the same reaction sequence to generate the diquinane **242** (Scheme 4.27).



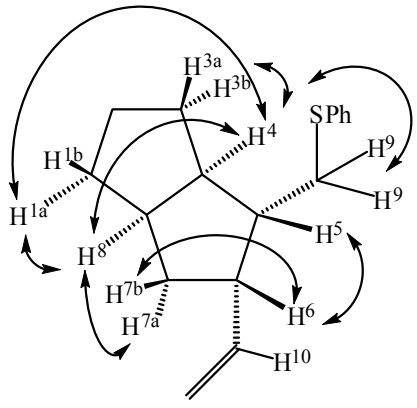
240 **241** **242**, 76%

Scheme 4.27. Iteration of the zinc-ene cyclization of a diallylzinc in combination with a γ-allylic substitution reaction.

The stereochemistry of **242** was assigned based on the 2D NMR spectra of a simpler conversion product **243** of its precursor **241** (Scheme 4.28). The important NOESY correlations found between 8-H and protons 7a-H, 4-H and 1a-H as well as between 4-H and protons 1a-H, 9-H (both) and 3b-H confirmed that the corresponding protons are in the same face of the molecule **243** (Scheme 428). On the other hand, other important NOESY correlations were found between 6-H and protons 5-H, and 7b-H, which indicate that the corresponding protons are in the opposite face of the molecule **243** to 8-H and 4-H (Scheme 428). No correlation signals were detected between 6-H and protons 7a-H, 8-H and 9-H as well as between 5-H and protons 4-H, 7a-H, and 8-H. All this evidence led to formula **243** with stereochemistry indicated in Scheme 4.28.



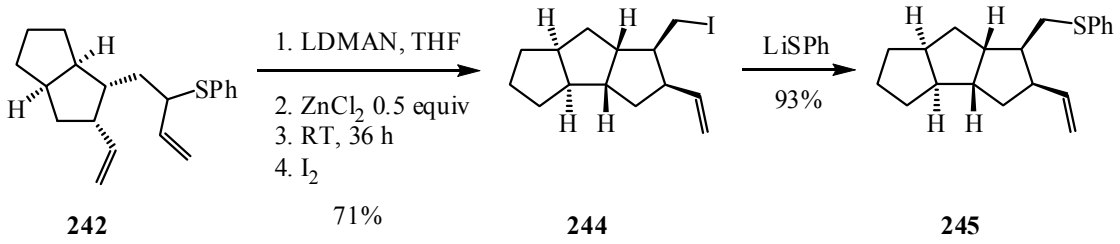
240 **241** **243**, 56%



243

Scheme 4.28. NOESY cross peaks for **243**.

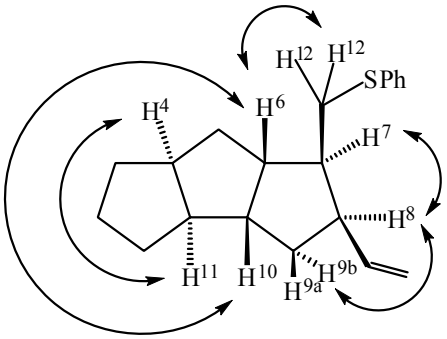
It is obvious that product **242** can be subjected to the same set of one-pot reactions to afford a triquinane framework **244** (Scheme 4.29). The iodide **244** was immediately converted to the more stable sulfide **245** without any further purification.



242 **244** **245**

Scheme 4.29. Zinc-ene cyclization of a diallylzinc in combination with a γ-allylic substitution reaction.

The stereochemistry of **245** was assigned based on the 2D NMR spectra (Scheme 4.30).



245

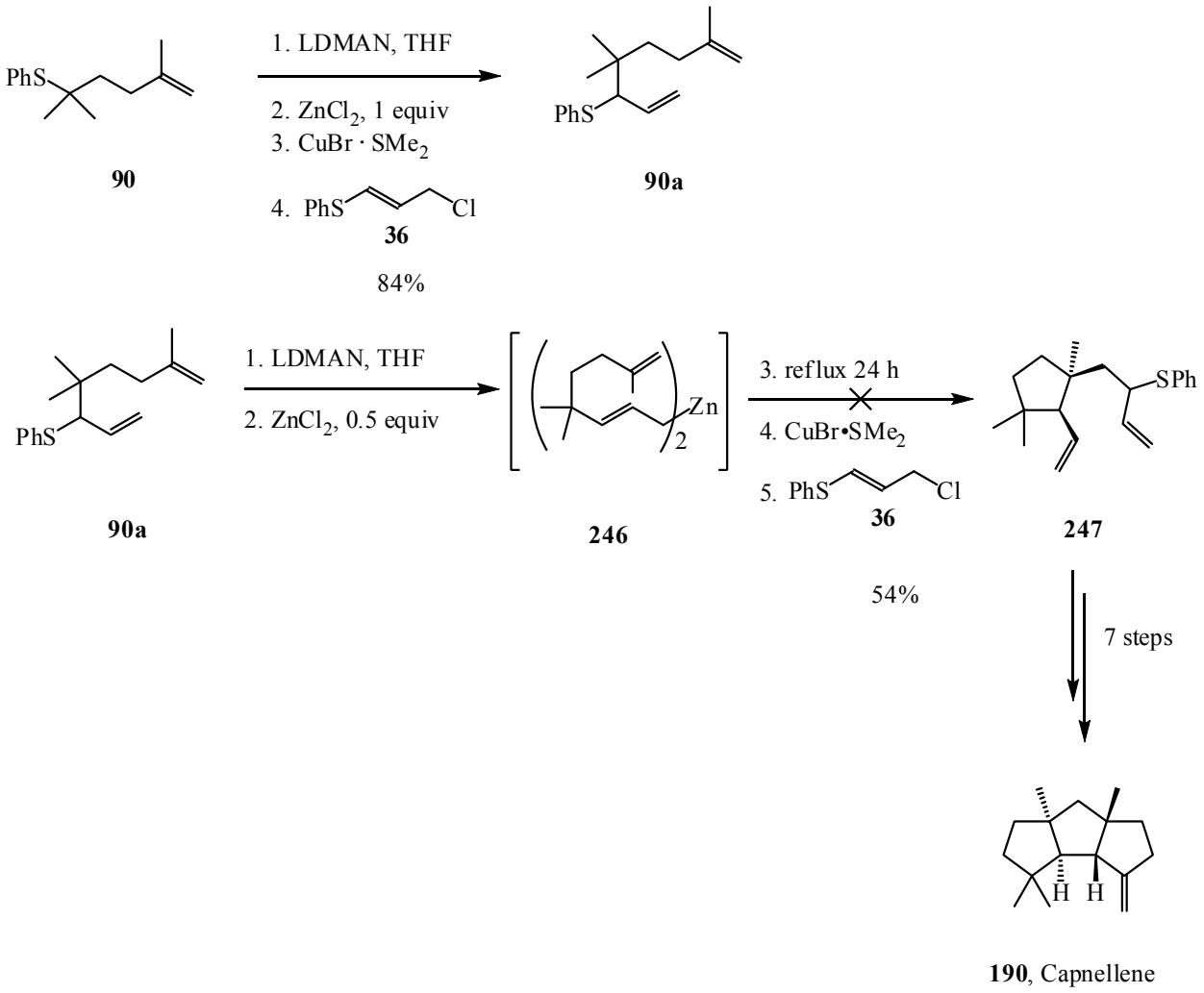
Scheme 4.30. NOESY cross peaks for **245**.

The important NOESY correlations found between 8-H and protons 7-H, 11-H and 4-H as well as between 7-H and proton 11-H confirming that the corresponding protons are in the

same face of the molecule **245** (Scheme 4.30). On the other hand, other important NOESY correlations were found between 6-H and protons 12-H (both), and 9a-H as well as between 9a-H and protons 12-H (both), which indicates that the corresponding protons are in the opposite face of the molecule **245** to 7-H and 8-H (Scheme 4.30). No correlation signals were detected between 7-H and protons 9a-H, 10-H and 6-H as well as between 10-H and protons 4-H, 11-H, 9b-H, and 8-H. All these evidences led to formula **245** with stereochemistry indicated in Scheme 4.30.

Consequently, the reaction sequence, which consists of the reductive lithiation of an allylic sulfide bearing a suitably placed vinyl group, transmetallation with zinc halide, zinc-ene cyclization followed by γ-allylic substitution, can be recognized as the heart of a novel iterative approach to ring-fused natural products, such as polyquinanes.

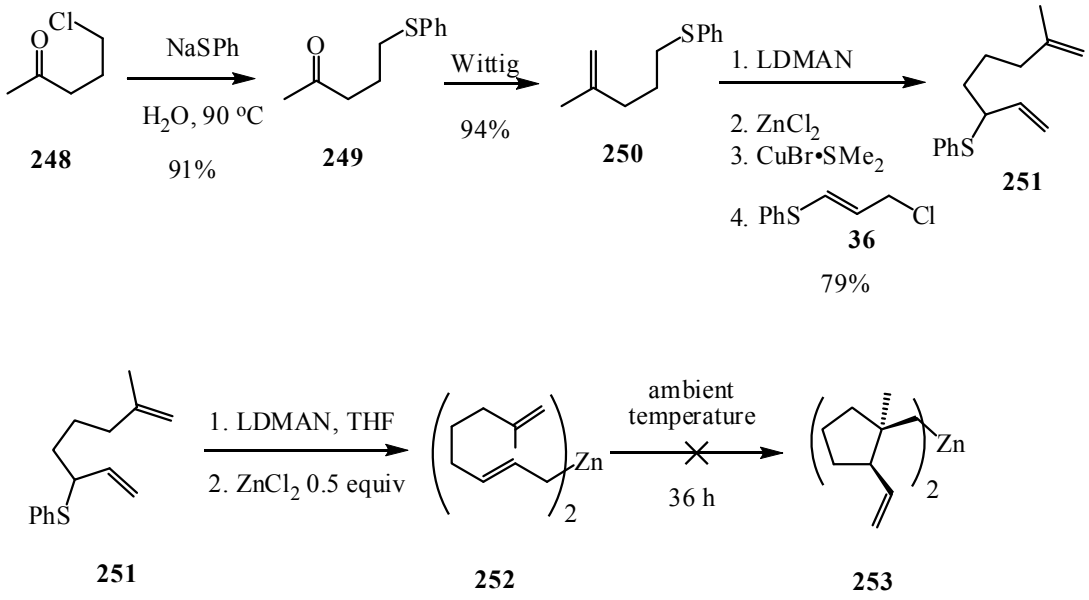
The idea of iterative synthetic methodology was partially exploited in the attempted formal synthesis of $\Delta^{9,12}$–capnellene **190**. The allylic sulfide **90a**, prepared by the γ-allylic substitution of the reductive lithiation product of **90** (Scheme 4.31), was utilized as the starting substrate (Scheme 4.31).



Scheme 4.31. Formal synthesis of $\Delta^{9,12}$ – capnellene exploiting iterative synthetic methodology.

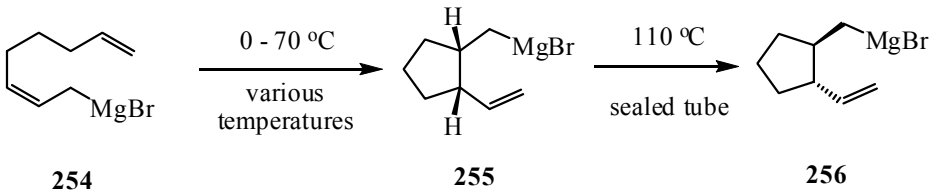
Unfortunately, our preliminary results indicate that the zinc-ene cyclization, which was expected to convert the allylic sulfide **90a** into the cyclized product **247**, proceeds in only moderate yield in 24 h and requires reflux conditions, probably due to the steric disadvantage created by the methyl group at the enophile vinyl group of **90a** (Scheme 4.31). The obtained product mixture apparently consists of *cis* and *trans* isomers of **247** as well as unreacted residue of **36** (Scheme 4.31). This mixture could not be analyzed completely. This assumption that

zinc-ene cyclization is affected by the methyl substituent at the enophile vinyl group was confirmed by the attempt of a failed cyclization of **251** at room temperature in 36 h (Scheme 4.32). No cyclized product was observed after the addition of iodine as an electrophile to trap the product.



Scheme 4.32. Failed cyclization of **251** possessing a methyl substituent at vinyl group

Formation of the mixture of *cis* and *trans* isomers of **247** can be explained by possible reversibility of the zinc-ene cyclization reaction. The reversibility of an intramolecular metallo-ene cyclization is precedented by epimerization of the *cis*-(2-vinylcyclopentyl)methylmagnesium bromide **255** into the more stable trans isomer **256** during heating at 110 °C (Scheme 4.33).[192] Several other examples of reversible magnesium-ene cyclization are given by Oppolzer in his review published in 1989.[158a]



254 **255** **256**

Scheme 4.33. Reversibility of intramolecular magnesium-ene cyclization.

In order to overcome the "zinc-ene cyclization reversibility" problem, it seems to be necessary to use the magnesium-ene cyclization, which in this particular case proceeds at a lower temperature then the zinc-ene cyclization.[164] The desired allylmagnesium substrate can be prepared either by direct magnesiation of the allylic sulfide **90a**, using the Mg-anthracene-THF complex,[169] or by reductive lithiation with LDMAN followed by transmetallation with a magnesium halide. The latter approach requires one more transmetallation with $ZnCl_2$ when the magnesium-ene cyclization is accomplished.

On the other hand, the easy reversibility of the intramolecular zinc-ene cyclization in comparison with the magnesium-ene cyclization can be considered as an important advantage of this reaction over the analogous magnesium-ene cyclization since the zinc-ene cyclization could lead to *cis* or *trans* products selectively under very mild conditions, such as reflux in a regular flask in THF. This dramatically expands the library of possible ring-fused frameworks, which could be prepared by the proposed iterative approach.

4.2.1 Conclusions

In the present work, we have demonstrated that intramolecular zinc-ene cyclizations require diallyl- or allyl alkylzincs as substrates and do not occur in the cases in which allylzinc

halides are involved. One of the important consequences of this fact is that the zinc-ene cyclization of diallylzincs is more sensitive to steric hindrance elaborated in the cyclic transition state. Thus, a proximate methyl substituent on the enophilic vinyl group appears to be large enough to block the ene-cyclization completely in the diallylzinc cyclization case.

Furthermore, the iterative synthetic approach to five membered ring-fused natural products, which is based on the reductive lithiation of an allylic sulfide bearing a suitably placed vinyl group with LDMAN and zinc-ene cyclization followed by γ-allylic substitution, has been developed and certain di- and triquinanes have been successfully synthesized.

Finally, it has been shown that the zinc-ene cyclization is an easily reversible process, which happens slowly at reflux conditions in a THF solution. This simple discovery can possibly be used as an important advantage of the zinc-ene cyclization, which may be able to expand dramatically the library of possibly available ring-fused frameworks either of *cis* or *trans* configuration.

4.3 EXPERIMENTAL SECTION

Instrumentation. ^{1}H and ^{13}C NMR and the 2D NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C at 22 °C. Chemical shift data are reported in units of δ (ppm) relative to internal standard TMS (set to 0 ppm). Chemical shifts for ^{13}C are referenced to the central peak of the $CDCl_3$ triplet (set to 77.0 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hz. High resolution mass spectra were recorded on a CH-5 double focusing Varian MAT or on VG 70-SE mass spectrometer.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled over sodium metal in the presence of benzophenone as indicator. Hexane and dichloromethane were distilled over CaH_2.

General Experimental Procedures. All reactions were carried out under a positive pressure of dry argon gas in oven-dried (140 °C) flasks and standard precautions against moisture were taken. Flash column chromatography (low pressure) was performed either with Silicycle Silia-P Flash silica gel (40-63 μm, surface area – 500 m^2/g) or with Sigma-Aldrich aluminum oxide (basic, 150 mesh, 58 Å, activated). Thin-layer chromatography was performed on glass supported 250 μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one of the following: 254 nm UV light and aqueous solution of $KMnO_4$ (1%) with NaOH (1%) and K_2CO_3 (6%). A dry ice/acetone bath was used to obtain temperatures of –78 °C. An acetone bath equipped with a cryogenic cooler Flexi-Cool FC-100 was used to obtain -55 ± 3 °C (the observed difference between the in-bath and the in-flask temperatures has never been greater than 1 °C for a 250 mL round bottom flask used in all radical-anion experiments). An ice bath was used to obtain 0 °C. Anhydrous magnesium sulfate was used as the drying reagent.

4,4,7-Trimethyl-3-phenylthio-1,7-octadiene (90a).

A solution of 2.80 g (12.8 mmol) of 2,5-dimethyl-5-phenylthio-1-hexene (**90**) in 5 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (26.8 mmol in 40 mL of THF) at -78 °C. The reaction mixture was stirred for 30 min at that temperature and then a 0.5 M THF solution of $ZnCl_2$ (26.0 mL, 13.0 mmol) was added. The reaction mixture was stirred for 40 min at -78 °C and then the acetone/dry-ice bath was removed. After the mixture had been

stirred at ambient temperature for about 30 min, 2.88 g (14.0 mmol) of CuBr•SMe_2 was added in one portion at room temperature. The reaction mixture was stirred for 10 min at that temperature and then the flask was cooled to -78 °C and a solution of 1.84 g (10.0 mmol) of 1-phenylthio-3-chloropropene (**36**) in 5 mL of THF was added via syringe. The reaction mixture was stirred and warmed slowly to the room temperature overnight before it was poured into 200 mL of saturated aqueous K_2CO_3. The reaction mixture was filtered through a celite pad and the filtrate was washed with 240 mL of 5% aqueous HCl and then with 200 mL of a saturated aqueous K_2CO_3. The product was extracted with diethyl ether and the extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 2.2 g (84% yield) of 4,4,7-trimethyl-3-phenylthio-1,7-octadiene (**90a**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.37 – 7.34 (m, 2 H), 7.20 – 7.16 (m, 3 H), 5.80 (ddd, 1 H, J_1 = 16.9 Hz, J_2 = 10.0 Hz, J_3 = 10.0 Hz), 4.84 (dd, 1 H, J_1 = 10.0 Hz, J_2 = 1.7 Hz), 4.69 – 4.59 (m, 3 H), 3.33 (d, 1 H, J = 10.0 Hz), 2.03 – 1.96 (m, 2 H), 1.71 (s, 3 H), 1.69 – 1.50 (m, 2 H), 1.08 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 145.9, 135.9, 135.6, 133.0, 128.4, 126.8, 115.5, 109.7, 64.4, 38.9, 36.5, 31.8, 25.1, 24.9, 22.5; exact mass calcd. for $C_{17}H_{24}S$ 260.1599, found 260.1595.

3-Phenylthio-1,7-octadiene (231).[193]

To a stirred solution of allyl phenylsulfide **33** (4.90 g, 33.0 mmol) in 150 mL of dry THF at -78 °C was added dropwise 21.1 mL (33.8 mmol) of a 1.6 M hexane solution of *n*-BuLi. After 1 h of stirring at that temperature, 5.00 g (33.6 mmol) of 5-bromo-1-pentene was added via syringe and the reaction mixture was stirred for an additional 3 h under "no light conditions". A saturated aqueous solution of K_2CO_3 (ca. 50 mL) was added to quench the reaction at -78 °C.

The product was extracted with ether (3×50 mL). The combined organic layer was washed with saturated brine solution and dried over $MgSO_4$. The organic solvents were removed by rotary evaporation at 45 °C under "no light conditions". The crude residue was chromatographed over silica gel (100% hexanes) to afford 5.4 g of diene **231** (88% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.37 – 7.17 (m, 5 H), 5.83 – 5.61 (m, 2 H), 5.00 – 4.80 (m, 4 H), 3.58 – 3.50 (m, 1 H), 2.01 (m, 2 H), 1.70 – 1.49 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 138.8, 138.1, 134.8, 132.6, 128.4, 126.8, 115.4, 114.7, 52.1, 33.5, 33.3, 26.4.

Preparation of c*is*-1-(iodomethyl)-2-vinylcyclopentane (236) through the cyclization of bis(2,3-octadienyl)zinc (238).

A solution of 2.18 g (10.0 mmol) of 3-phenylthio-1,7-octadiene (**231**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (20.8 mmol in 40 mL of THF) at -78 °C. The reaction mixture was stirred for 40 min at that temperature and then a 0.5 M THF solution of $ZnCl_2$ (10.0 mL, 5.0 mmol) was added. The reaction mixture was stirred for 40 min at -78 °C and then the acetone/dry-ice bath was removed. After the mixture had been stirred at ambient temperature for 36 h, 5.05 g (20.0 mmol) of iodine was added in one portion at 0 °C and then the ice/water bath was removed. The reaction mixture had been stirred for 20 min at ambient temperature before it was poured into 200 mL of a saturated aqueous K_2CO_3. As much solid sodium thiosulfate was added as was necessary to remove the color and the organic product was extracted with ether. The extract was washed in a separatory funnel three times with ca. 30 mL of 3 M HCl to remove DMAN and then with 100 mL of a saturated aqueous K_2CO_3. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 1.8 g (76% yield) of *cis*-1-

(iodomethyl)-2-vinylcyclopentane (**236**). ^{1}H NMR ($CDCl_3$) δ (ppm): 5.76 – 5.64 (m, 1 H), 5.11 (dd, 1 H, J_1 = 18.0 Hz, J_2 = 1.0 Hz), 5.06 (dd, 1 H, J_1 = 12.0 Hz, J_2 = 1.2 Hz), 3.15 – 3.04 (m, 2 H), 2.74 – 2.65 (m, 1 H), 2.42 – 2.32 (m, 1 H), 1.98 – 1.60 (br, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 137.5, 115.7, 47.3, 47.0, 31.6, 31.1, 23.0, 9.8; exact mass calcd. for $C_8H_{13}I$ 236.0062, found 236.0062.

Preparation of c*is*-1-(iodomethyl)-2-vinylcyclopentane (236) through the cyclization of 2,7-octadienyl ethylzinc (234).

A solution of 2.60 g (12.0 mmol) of 3-phenylthio-1,7-octadiene (**231**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (25.0 mmol in 40 mL of THF) at -78 °C. The reaction mixture was stirred for 40 min at that temperature and then a 0.5 M THF solution of $ZnCl_2$ (24.0 mL, 12.0 mmol) was added. The reaction mixture was stirred for 40 min at -78 °C and then a 0.5 M benzene/cyclohexane (9:1) solution of EtLi (24.0 mL, 12.0 mmol) was added dropwise. The reaction mixture was allowed to stir at -78 °C for 40 min. The acetone/dry-ice bath was removed and, after the mixture had been stirred at ambient temperature for 36 h, 12.70 g (50.0 mmol) of iodine was added to the reaction mixture in one portion at 0 °C and then the ice/water bath was removed. The reaction mixture was stirred for 20 min at an ambient temperature before it was poured into 200 mL of a saturated aqueous K_2CO_3. As much solid sodium thiosulfate was added as was necessary to remove the color and the organic product was extracted with ether. The extract was washed in a separatory funnel three times with ca. 30 mL of 3 M HCl to remove DMAN and then with 100 mL of a saturated aqueous K_2CO_3. The extract was dried over $MgSO_4$ and then concentrated in vacuo at 55 – 60 °C. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 1.2 g (42% yield) of *cis*-1-

(iodomethyl)-2-vinylcyclopentane (**236**). The ^{1}H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$) spectra and elemental analysis of (**236**) are given above.

***cis*-1-(Phenylthiomethyl)-2-vinylcyclopentane (237).**

A 1.6 M hexane solution of *n*-BuLi (3.0 mL, 4.8 mmol) was added dropwise to a solution of 0.51 mL (5.0 mmol) of thiophenol in 10 mL of dry THF at 0 °C. The reaction mixture was stirred at that temperature for 15 min and then a solution of 1.00 g (4.8 mmol) of *cis*-1-(iodomethyl)-2-vinylcyclopentane (**236**) in 5 mL of THF was added dropwise. The reaction mixture was allowed to warm to ambient temperature and to stir overnight and then the reaction was quenched with 100 mL of saturated aqueous K_2CO_3. The organic product was extracted with ether, and the extract was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 0.90 g (98% yield) of the desired *cis*-1-(phenylthiomethyl)-2-vinylcyclopentane (**237**). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.30 – 7.07 (m, 5 H), 5.79 – 5.69 (ddd, 1 H, J_1 = 18.0 Hz, J_2 = 12.0 Hz, J_3 = 9.0 Hz), 5.07 – 5.00 (m, 2 H), 2.96 (dd, 1 H, J_1 = 12.0 Hz, J_2 = 6.0 Hz), 2.74 – 2.64 (m, 2 H), 2.16 – 1.86 (m, 1 H), 1.86 – 1.44 (br, 6 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 138.5, 137.3, 128.6, 128.5, 125.3, 115.1, 46.8, 42.9, 35.5, 30.7, 30.2, 22.8. These NMR data agreed well with Shirong's spectra.[191] Exact mass calcd. for $C_{14}H_{18}S$ 218.1129, found 218.1125.

***cis*-1-(2-Phenylthio-3-butenyl)-2-vinylcyclopentane (240).**

A solution of 6.00 g (27.5 mmol) of 3-phenylthio-1,7-octadiene (**231**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (57.8 mmol in 80 mL of THF) at -78 °C. The reaction mixture was stirred for 1 h at that temperature and then 28.0 mL

(13.8 mmol) of a 0.5 M THF solution of $ZnCl_2$ was added slowly. The reaction mixture was stirred for 30 min at -78 °C and then the acetone/dry-ice bath was removed. After the reaction mixture had been stirred at ambient temperature for 36 h, 6.20 g (30.0 mmol) of $CuBr•SMe_2$ was added in one portion at ambient temperature. The reaction mixture was allowed to stir for 15 min at that temperature and then it was cooled to -78 °C. A solution of 4.10 g (22.5 mmol) of 1-phenylthio-3-chloropropene **36** in 10 mL of dry THF was added at that temperature. The reaction mixture was allowed to warm slowly to ambient temperature overnight and then the reaction was quenched with 200 mL of saturated aqueous K_2CO_3. The reaction mixture was filtered through a celite pad and the filtrate was washed with 240 mL of 5% aqueous HCl and then with 200 mL of saturated aqueous K_2CO_3. The product was extracted with diethyl ether and the extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 4.7 g (81% yield) of *cis*-1-(2-phenylthio-3-butenyl)-2-vinylcyclopentane (**240**) as a colorless oil (a mixture of two diastereomers). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.38 – 7.19 (m, 5 H), 5.75 – 5.60 (m, 2 H), 5.03 – 4.77 (m, 4 H), 3.66 – 3.52 (m, 1 H), 2.65 – 2.50 (m, 1 H), 2.30 – 1.97 (m, 2 H), 1.81 – 1.45 (br, 7 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 139.6, 139.2, 138.9, 134.8, 134.7, 132.9, 132.6, 128.5 (2C), 126.9 (2C), 115.3, 115.1, 114.3, 51.4, 51.3, 47.0, 46.3, 41.2, 41.0, 35.7, 35.6, 31.5, 31.3, 30.6, 30.0, 23.0, 22.8; exact mass calcd. for $C_{17}H_{22}S$ 258.1442, found 258.1447.

cis-1-(2-Phenylthio-3-butenyl)-2-vinyl-_cis_-octahydropentalene (242).

A solution of 3.97 g (15.4 mmol) of *cis*-1-(2-phenylthio-3-butenyl)-2-vinylcyclopentane (**240**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (32.3 mmol in 80 mL of THF) at -78 °C. The reaction mixture was stirred for 1 h at that temperature

and then 15.4 mL (7.7 mmol) of a 0.5 M THF solution of $ZnCl_2$ was added slowly. The reaction mixture was stirred for 30 min at -78 °C and then the acetone/dry-ice bath was removed. After the mixture had been stirred at ambient temperature for 36 h, 3.50 g (17.0 mmol) of CuBr•SMe_2 was added in one portion at ambient temperature. The reaction mixture was allowed to stir for 15 min at that temperature and then it was cooled to -78 °C. A solution of 3.40 g (18.5 mmol) of 1-phenylthio-3-chloropropene **36** in 10 mL of dry THF was added at that temperature. The reaction mixture was allowed to slowly warm to ambient temperature overnight and then the reaction was quenched with 200 mL of saturated aqueous K_2CO_3. The reaction mixture was filtered through a celite pad and the filtrate was washed with 240 mL of 5% aqueous HCl and then again with 200 mL of saturated aqueous K_2CO_3. The product was extracted with diethyl ether and the extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 4.2 g (76% yield) of *cis*-1-(2-phenylthio-3-butenyl)-2-vinyl-*cis*-octahydropentalene (**242**) as a colorless oil (a mixture of two diastereomers). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.38 – 7.18 (m, 5 H), 5.97 – 5.05 (m, 2 H), 5.00 – 4.82 (m, 4 H), 3.72 – 3.05 (m, 1 H), 2.72 – 2.37 (br, 2 H), 2.20 – 1.26 (br, 12 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 139.2, 139.1, 138.8, 134.8, 134.7, 132.9, 132.7, 128.5 (2C), 126.9 (2C), 115.5, 114.8, 114.4, 51.0, 50.8, 48.3, 48.1, 47.8, 47.7, 47.5, 47.4, 41.4, 41.3, 39.5, 39.1, 35.9, 35.6, 33.7, 33.5, 32.7, 32.5, 25.8, 25.5; exact mass calcd. for $C_{20}H_{26}S$ 298.1755, found 298.1746.

cis-1-(Phenylthiomethyl)-2-vinyl-_cis_-octahydropentalene (243).

A solution of 3.42 g (13.3 mmol) of *cis*-1-(2-phenylthio-3-butenyl)-2-vinylcyclopentane (**240**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (27.8 mmol in 80 mL of THF) at -78 °C. The reaction mixture was stirred for 1 h at that temperature

and then 13.3 mL (6.7 mmol) of a 0.5 M THF solution of $ZnCl_2$ was added slowly. The reaction mixture was stirred for 30 min at -78 °C and then the acetone/dry-ice bath was removed. After the reaction mixture had been stirred at ambient temperature for 36 h, 11.40 g (44.9 mmol) of iodine was added to the reaction mixture in one portion at 0 °C and then the ice/water bath was removed. The reaction mixture had been stirred for 20 min at ambient temperature before it was poured into 200 mL of saturated aqueous K_2CO_3. As much solid sodium thiosulfate was added as was necessary to remove the color and the organic product was extracted with ether. The extract was washed in a separatory funnel three times with ca. 50 mL of 3 M HCl to remove DMAN and then with 200 mL of saturated aqueous K_2CO_3. The extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 2.2 g (60% yield) of *cis*-1-(iodomethyl)-2-vinyl-*cis*-octahydropentalene as a yellow oil. Elemental analysis: exact mass calcd. for $C_{11}H_{17}I$ 276.0375, found 276.0372.

A 1.7 M pentane solution of *t*-BuLi (4.4 mL, 7.5 mmol) was added dropwise to a solution of 0.77 mL (7.5 mmol) of thiophenol in 10 mL of dry THF at 0 °C. The reaction mixture had been stirred for 15 min at that temperature before a solution of 1.89 g (6.9 mmol) of *cis*-1-(iodomethyl)-2-vinyl-*cis*-octahydropentalene in 5 mL of THF was added dropwise at 0 °C. The reaction mixture was allowed to stir and warm slowly to ambient temperature overnight and then it was poured into 100 mL of 1 M aqueous NaOH. The product was extracted with dichloromethane and the extract was washed with brine. The extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 1.65 g (94% yield) of the titled product **243** as a colorless oil (one diastereomer). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.30 – 7.09 (m, 5 H), 5.77 (ddd, 1 H, J_1 = 17.1 Hz, J_2 = 9.6 Hz, J_3 = 9.6 Hz), 5.11 – 4.97 (m, 2 H), 2.87 – 2.76 (m, 2 H), 2.63 – 2.57 (m, 1 H), 2.27 –

2.19 (m, 1 H), 1.84 – 1.25 (br, 10 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 138.2, 137.5, 128.7, 128.3, 125.3, 115.6, 49.6, 48.1, 47.6, 41.6, 38.5, 35.5, 33.7, 32.8, 25.5; exact mass calcd. for $C_{17}H_{22}S$ 258.1442, found 258.1444.

Racemic (1*S*,2*R*,3a*R*,3b*S*,6a*S*,7a*S*)-1-(Phenylthiomethyl)-2-vinyldecahydro-1*H*-cyclopenta-[*a*]pentalene (245).

A solution of 2.98 g (10.0 mmol) of *cis*-1-(2-phenylthio-3-butenyl)-2-vinyl-*cis*-octahydropentalene (**242**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (21.0 mmol in 80 mL of THF) at -78 °C. The reaction mixture was stirred for 1 h at that temperature and then 10.0 mL (5.0 mmol) of a 0.5 M THF solution of $ZnCl_2$ was added slowly. The reaction mixture was stirred for 30 min at -78 °C and then the acetone/dry-ice bath was removed. After the mixture had been stirred at ambient temperature for 36 h, 7.60 g (30.0 mmol) of iodine was added in one portion at 0 °C and then the ice/water bath was removed. The reaction mixture was stirred for 20 min at an ambient temperature before it was poured into 200 mL of saturated aqueous K_2CO_3. As much solid sodium thiosulfate was added as was necessary to remove the color and the organic product was extracted with ether. The extract was washed in a separatory funnel three times with ca. 50 mL of 3 M HCl to remove DMAN and then with 200 mL of a saturated aqueous K_2CO_3. The extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed in a short column over basic alumina (100% hexane) to afford 2.3 g (71% yield) of the racemic version of (1*S*,2*R*,3a*R*,3b*S*,6a*S*,7a*S*)-1-(iodomethyl)-2-vinyldecahydro-1*H*-cyclopenta[*a*]pentalene (**244**), which was immediately converted to the corresponding sulfide **245** without any further purification.

A 1.7 M pentane solution of *t*-BuLi (4.6 mL, 7.8 mmol) was added dropwise to a solution of 0.82 mL (8.0 mmol) of thiophenol in 10 mL of dry THF at 0 °C. The reaction mixture was stirred for 15 min at that temperature and a solution of 2.30 g (7.3 mmol) of **244** in 5 mL of THF was added dropwise at 0 °C. The reaction mixture was allowed to stir and warm slowly to an ambient temperature overnight and then it was poured into 100 mL of a 1 M aqueous NaOH. The product was extracted with dichloromethane and the extract was washed with brine, dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 2.0 g (93% yield) of the titled product **245** as a colorless oil (one diastereomer). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.29 – 7.11 (m, 5 H), 5.76 (ddd, 1 H, J_1 = 17.4 Hz, J_2 = 9.3 Hz, J_3 = 8.4 Hz), 5.08 – 4.99 (m, 2H), 2.87 – 2.79 (m, 3 H), 2.46 – 2.36 (m, 3 H), 2.00 – 1.30 (br, 12 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 138.4, 137.2, 128.7, 128.3, 125.3, 115.4, 53.4, 49.9, 49.2, 49.1, 47.5, 44.4, 38.8, 38.6, 35.3, 32.8, 31.3, 25.4; exact mass calcd. for $C_{20}H_{26}S$ 298.1755, found 298.1750.

5-Phenylthio-2-pentanone (249).

A 500 mL three-neck round-bottom flask equipped with condenser, addition funnel and glass stopper was charged with 250 mL of water and 8.4 g (210 mmol) of NaOH. Thiophenol (22.0 mL g, 210 mmol) was added to the solution slowly. The reaction mixture was stirred for 30 min to insure the complete formation of sodium thiophenoxide. Commercially available technical 5-chloro-2-pentanone **248** (25.0 g, 210 mmol) was added slowly at room temperature. The resulting reaction mixture was stirred at 90 °C for 3 h, and then it was cooled to an ambient temperature. The product was extracted with dichloromethane. The organic extract was washed with 200 mL of a 1 M aqueous solution of NaOH and then with brine. The extract was dried

over magnesium sulfate and concentrated in vacuo. The crude residue was chromatographed over silica gel (30% EtOAc/hexane) to afford 37.0 g (91% yield) of the desired 5-phenylthio-2-pentanone (**250**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.30 – 7.08 (m, 5 H), 2.86 (t, 2 H, *J* = 7.2 Hz), 2.49 (t, 2 H, *J* = 7.0 Hz), 2.02 (s, 3 H), 1.87 – 1.78 (m, 2 H); ^{13}C NMR ($CDCl_3$), δ (ppm): 207.0, 135.8, 128.3 (2C), 125.2, 41.2, 32.0, 29.3, 22.4; exact mass calcd. for $C_{11}H_{14}OS$ 194.0765, found 194.0765.

2-Methyl-5-phenylthio-1-pentene (250).

To a suspension of methyl triphenylphosphonium bromide (64.2 g, 180 mmol) in THF (600 mL), a 1.6 M hexane solution of *n*-butyllithium (104 mL, 166 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 min; it was then cooled to -78 °C and a solution of 5-phenylthio-2-pentanone (**249**) (19.4 g, 100 mmol) in THF (100 mL) was added dropwise. After being stirred at -78 °C for 1 h, the reaction mixture was warmed to 0 °C, stirred for 2 h, and the reaction was quenched with 10 mL of methanol. The mixture was poured into 2 L of pentane and filtered through a silica gel pad. The organic solvents were removed by rotary evaporation. Flash chromatography (5% EtOAc/hex) provided the titled product **250** as a colorless oil 18.0 g (94% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.27 -7.11 (m, 5 H), 4.72 (s, 1 H), 4.68 (s, 1 H), 2.88 (t, 2 H, *J* = 7.2 Hz), 2.13 (t, 2 H, *J* = 7.2 Hz), 1.81 – 1.71 (m, 2 H), 1.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 144.5, 136.7, 129.0, 128.7, 125.7, 110.6, 36.6, 33.0, 26.9, 22.2; exact mass calcd. for $C_{12}H_{16}S$ 192.0973, found 192.0971.

2-Methyl-6-phenylthio-1,7-octadiene (251).

A solution of 6.90 g (36.0 mmol) of 2-methyl-5-phenylthio-1-pentene (**250**) in 10 mL of dry THF was added dropwise to a solution of freshly prepared LDMAN (75.4 mmol in 120 mL of THF) at -78 °C. The reaction mixture was stirred for 1 h at that temperature and then a 0.5 M THF solution of $ZnCl_2$ (72.0 mL, 36.0 mmol) was added. The reaction mixture was stirred for 30 min at -78 °C and then the acetone/dry-ice bath was removed. After the mixture had been stirred at ambient temperature for about 30 min, 8.20 g (39.6 mmol) of CuBr•SMe_2 was added in one portion at room temperature. The reaction mixture was stirred for 15 min at ambient temperature and then the flask was cooled to -78 °C and a solution of 5.9 g (32.0 mmol) of 1-phenylthio-3-chloropropene (**36**) in 10 mL of THF was added via syringe. The reaction mixture had been allowed to stir and warm slowly to the room temperature overnight before it was poured into 200 mL of a saturated aqueous K_2CO_3. The reaction mixture was filtered through a celite pad and the filtrate was washed with 240 mL of 5% aqueous HCl and then with 200 mL of saturated aqueous K_2CO_3. The product was extracted with ether (3×50 mL). The extract was dried over $MgSO_4$ and then concentrated in vacuo. The crude residue was chromatographed over silica gel (2.5% EtOAc/hexane) to afford 5.8 g (79% yield) of 2-methyl-6-phenylthio-1,7-octadiene (**251**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.37 – 7.19 (m, 5 H), 5.67 (ddd, 1 H, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 9.0 Hz), 4.92 (dd, 1 H, J_1 = 9.9 Hz, J_2 = 1.0 Hz), 4.85 (d, 1 H, J = 16.8 Hz), 4.70 – 4.67 (m, 2 H), 3.61 – 3.53 (m, 1 H), 2.01 (t, 2 H, J = 7.2 Hz), 1.69 (s, 3 H), 1.62 – 1.56 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 145.2, 138.8, 134.2, 132.6, 128.5, 126.9, 115.5, 110.2, 52.2, 37.3, 33.7, 25.1, 22.2; exact mass calcd. for $C_{15}H_{20}S$ 232.1286, found 232.1286.

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[54] Some authors[19] write this Schlenk equilibrium with $\mathbf{ZnR_2 \bullet ZnCl_2}$ as the product and others[17] with $\mathbf{ZnR_2}$ as the product, while Dessy[18] shows the same equilibrium. We are not aware of any studies that establish which of these forms of dialkylzinc is present in the case of the chlorides.

[55] CuCN must be used with considerable care and disposing of the used material is a significant environmental hazard, particularly if used in a large-scale industrial operation. On the other hand, CuSPh, while admittedly somewhat less stable, allows the recovery of the thiophenol by acidification and distillation. Consideration of operational simplicity and cost also favor CuSPh, which can be used as purchased, whereas $CuCN \bullet (LiCl)_2$ must be prepared from the two reagents; anhydrous LiCl is very expensive and so the reagent is considerably more expensive per mole than CuSPh.

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