Enantioselective Conjugate Addition Reactions to α,β-Unsaturated-β,γ-Substituted-2,5-Cyclohexadienones

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By

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Abstract

Enantioselective conjugate addition (ECA) reactions between organometallic reagents and cyclohexadienone **165** are being investigated. Previous studies have shown that ECAs, of organometallic reagents to α,β-unsaturated cyclohexadienones, are useful in many natural product syntheses. The substrates used in earlier studies were simple 2,5-cyclohexadienones, with a proton at the C-3 position, resulting in the synthesis of a trisubstituted C-3 atom. ECAs that afford all-carbon quaternary stereogenic centers are a much more challenging problem and few examples have been reported. Some natural products contain a γ-hydroxy group, however, no ECA substrates have incorporated this motif. ECAs have been accomplished with substrates having a γ-ether substituent. The cyclohexadienone **165** system presents three challenging problems to overcome for an ECA reaction: the tertiary methyl substituents at the 3 and 5 positions, facial selectivity and enantioselectivity. An ECA to **165** using an organoaluminum reagent and an external chiral ligand **26** was successful in producing a product that showed the reaction was moderately stereoselective. A diastereoselective conjugate addition reaction (DCA) to **165** using a chiral auxiliary **68** was also successful in producing a product that showed the reaction was moderately enantioenriched. Lastly, a variable temperature NMR study was performed to establish the presence of dynamic motions of the C=N bond present in sulfinyl imines **229** and **230.** As a result, the sulfinyl imines **229** and **230** were found to be interconverting at -78°C.

Acknowledgments

At the completion of this project I feel it necessary to thank a few people that helped to make this project possible.

Firstly, I would like to thank my family members, Michael, Gloria and Kyle. If it wasn't for their undying support from 3000 km away over the last two years I would have probably not made it this far.

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Many thanks are also extended to everyone else in Dr. Abrams' lab that helped me with the finer points of this project.

Lastly, my thanks must go to all of my friends in the west of Canada who endured with me throughout this project.

To Mom and Dad, the ones who sent me WEST…

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List of Abbreviations

ABA	abscisic acid
ACN	acetonitrile
Ac	acetyl
Ar	Arrhenius
Bn	benzyl
bp	boiling point
cap	caprolactam
Cbz	benzyloxycarbonyl
CG*	chiral non-transferable group
CI	chemical ionization
CIP	contact ion pair
CU	chiral unit
CuTC	copper (I) thiophene-2-carboxylate
DCM	dichloromethane
DDQ	dichloro dicyano quinone
DIPEA	*N*,*N*-diisopropylethylamine
DME	dimethyl ether
DMP	dimethyl phthalate
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DRIFT	diffuse reflectance cell
ee	enantiomeric excess; for a mixture of two enantiomers R and S, ee = $\lvert$ ([R]-[S])$\rvert$ /([R]+[S]) x 100%
ΔE_a	change in activation energy
ECA	enantioselective conjugate addition
EI	electron impact
Et	ethyl
eq	equivalent
er	enantiomeric ratio

Ey	Eyring
FCC	flash column chromatography
$\Delta G^{\ddagger}$	change in free energy
GC	gas chromatography
$\Delta H^{\ddagger}$	change in enthalpy
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
i-Pr	isopropyl
IR	infrared
k	rate constant
L*	chiral ligand
LDA	lithium diisopropylamide
M*	metal salt
Me	methyl
MEM	methoxyethoxymethyl ether
mol	mole
MOM	methoxymethyl ether
mp	melting point
MS	molecular sieves
n-Bu	*n*-butyl
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NMM	*N*-methylmorpholine
NR	no reaction
Nu	nucleophile
OTf	trifluoromethanesulfonate
PIDA	phenyliodine (III) diacetate
Ph	phenyl
pTLC	preparative thin layer chromatography
(R)-Binap	(R)-(+)-2,2'-Bis(diphenylphosphino)-1'1-binaphthyl

R	alkyl
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
RT	room temperature
$\Delta S^{\ddagger}$	change in entropy
SIP	separated ion pair
T	temperature
t	time
TBAF	tetrabutylammonium fluoride
TBHP	tert-butylhydroperoxide
t-butyl	tert-butyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
UV	ultraviolet
*	stereogenic center

CHAPTER 1: LITERATURE REVIEW OF STEREOSELECTIVE CONJUGATE ADDITION REACTIONS

1.1 Enantioselective Conjugate Addition (ECA)

Enantioselective syntheses have the potential to generate large quantities of chiral products with high enantioselectivities from small quantities of chiral catalysts. This characteristic of being a simple and atom-economic process, in comparison to enzyme catalysis, permits a much broader substrate scope and can provide access to both enantiomers of the product by simply switching the chirality of the chiral catalyst.[1] Processes such as the reduction of carbonyls, imines, and alkenes, additions to enones, enolate alkylations, aldol reactions, and cycloadditions, as well as sigmatropic rearrangements have all been tailored to yield non-racemic products.[2] Increased attention and financial importance has been granted to enantioselective synthesis methods as pharmaceutical companies are exchanging racemic drugs for non-racemic ones to extend the patents on profitable compounds.[3]

In the year 2001 the Nobel Prize in Chemistry was awarded to W. S. Knowles, R. Noyori, and K. B. Sharpless for their revolutionary developments of catalytic asymmetric hydrogenation and oxidation reactions. These developments of catalytic methods for asymmetric synthesis were amongst some of the foremost and unprecedented recent achievements of chemistry.[4] Many catalytic asymmetric oxidation and reduction methods have been developed. However, currently few catalytic asymmetric methods for constructing carbon-carbon (C-C) bonds have been developed.[5]

The formation of a C-C bond can be attained by a conjugate addition reaction (Figure 1).[6]

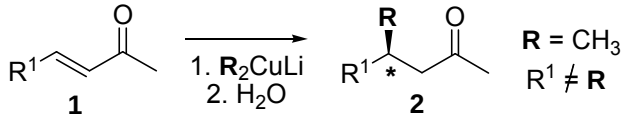


Figure 1. Conjugate addition reaction forming a C-C bond.

This reaction involves the addition of a carbon nucleophile **R** to a substituted double or triple bond conjugated to a carbonyl group as in **1**. Conjugate addition reactions can lead to the formation of a stereogenic center (*). The development of diastereoselective addition to chiral acceptor substrates to form a stereogenic center is an area of conjugate addition chemistry that has been well established.[7] On the other hand, much less is known about enantioselective conjugate additions (ECAs) of chirally modified nucleophiles to prochiral substrates or achiral substrates that can be converted to chiral products in a single step (Figure 2).[1]

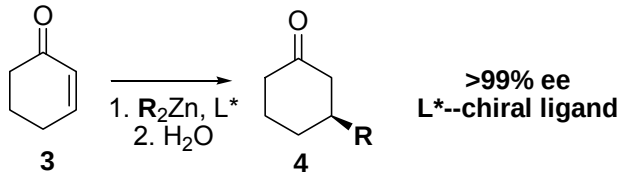


Figure 2. An example of enantioselective conjugate addition (ECA) reaction.

Conjugate addition of alkyl-containing reagents to α,β unsaturated organic substrates is an important method of assembling structurally complex organic molecules.[8] According to Seyden-Penne,[9] a conjugate addition reaction can achieve enantioselectivity through methods such as: 1) the use of a chiral non-transferable group (CG*) bonded to the nucleophile (Nu); 2) the use of an external chiral ligand (L*), which in turn complexes to the nucleophile (Nu); 3) the use of an external chiral ligand (L*) that joins to the acceptor compound and directs the nucleophile (Nu); 4) the use of an external chiral ligand (L*) and an external metal salt (M*) that directs in motion the acceptor compound to the nucleophile (Nu); 5) and the use of an external chiral unit (CU*) that unites collectively both the acceptor and donor compounds (Nu) (Figure 3). The final four methods presented allow the possibility of using catalytic amounts of a chiral component; however, the first method does not. Lastly, all the methods presented require a ligand or auxiliary as a chiral component.

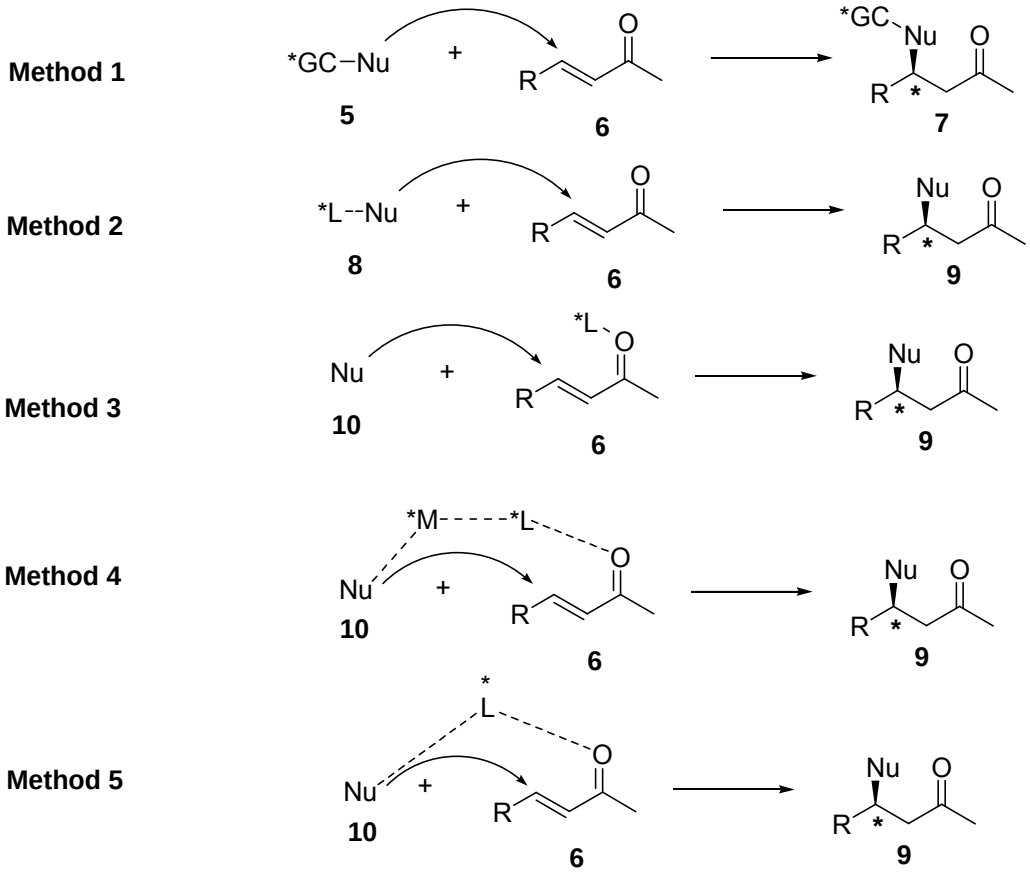


Figure 3. Seyden-Penne's classification of ECA methods.

The knowledge base of chemistry today provides ECA methods to create many tertiary stereocenters with excellent levels of enantiocontrol and chemical yields (Figure 4). Various methodologies for tailor-made ligands have been developed and are commonly used with a wide variety of acceptor substrates in organic synthesis.[1] ECAs forming tertiary stereocenters have been successfully applied to cyclic[10, 11] and acyclic enones,[12] lactones,[13] lactams,[14] nitro olefins,[15] amides[16] and malonates.[17] However, whatever the addition acceptor, many of these ECA reaction methods with β,β-disubstituted acceptors have failed.[18]

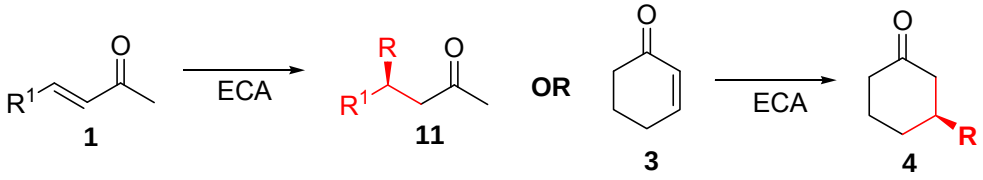


Figure 4. ECA to produce a tertiary stereocenter.

Carbon atoms bonded to four other carbon substituents are termed as all-carbon quaternary centers. The synthesis of these all-carbon quaternary centers is a gigantic challenge in modern chemistry, because the creation of these centers is complicated by steric repulsion between the carbon substituents.[1] Catalytic enantioselective methods that successfully produce a C-C bond of all-carbon quaternary stereocenters reactions are rare (Figure 5).

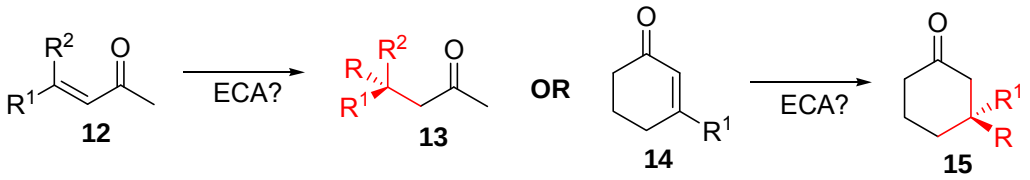
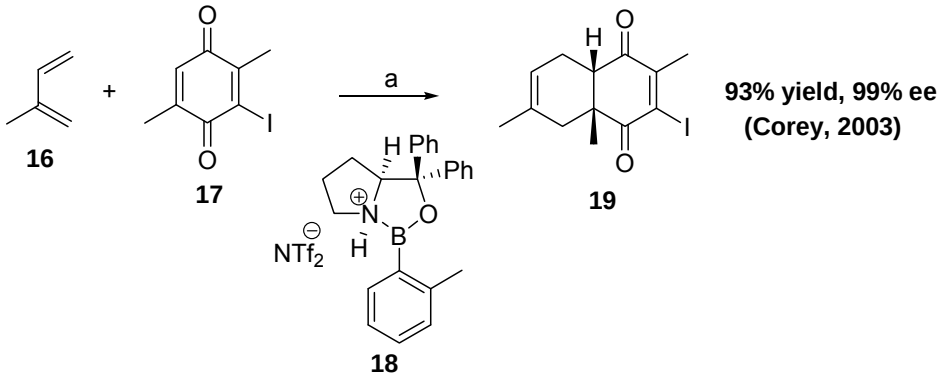


Figure 5. Hypothetical ECA to produce an all-carbon quaternary stereocenter.

Precedent C-C bond formation reactions that form all-carbon quaternary stereocenter are Diels-Alder cycloadditions, Pd-allylations reactions and conjugate additions (Figure 6).[4] One successful example using an ECA reaction method to synthesize an all-carbon quaternary stereocenter was reported by Alexakis[18] (Figure 6c). The construction of quaternary stereocenters still remains a significantly underdeveloped research area.

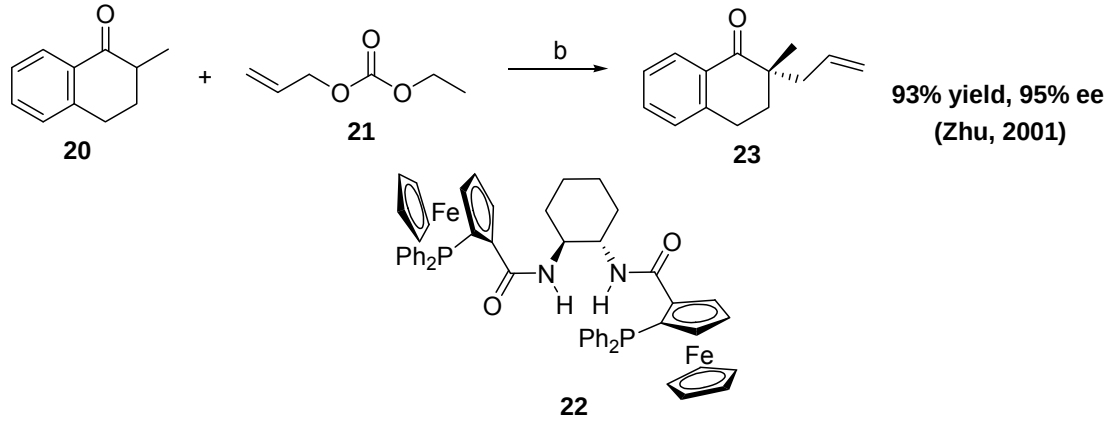
The goal of this research is to develop an ECA reaction to a specific class of α,β-unsaturated β-disubstituted γ-trisubstituted ketones based on previously reported ECA reactions to α,β-unsaturated β-disubstituted and α,β-unsaturated ketones. This study can be achieved through the synthesis of a simple α,β-unsaturated β-disubstituted γ-trisubstituted bearing small side groups. The 4-alkyl-4-hydroxy-3,5-dimethylcyclohexa-2,5-dienone system allows for this type of reaction. Furthermore, this type of system could be used as a model for other natural product syntheses. We hypothesized that existing ECA methods for sterically demanding substrates could be adapted to the 4-alkyl-4-hydroxy-3,5-dimethylcyclohexa-2,5-dienone system to produce an ECA product with high ee, yield and catalytic efficiency.

a) Diels-Alder Cycloaddition.



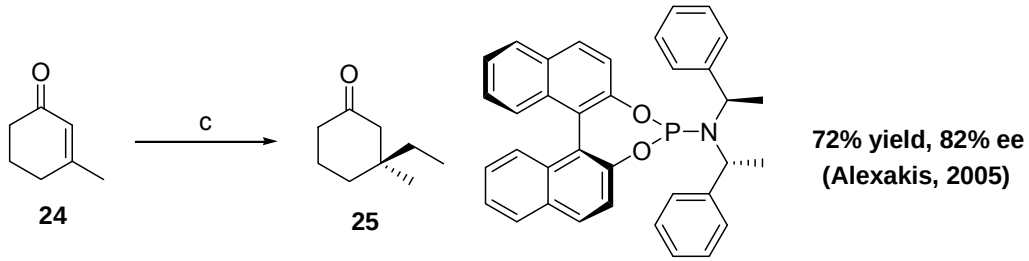
a) 20 mol % (**18**), CH_2Cl_2, -78°C.

b) Pd Allylation.



b) 7.5 mol % (**22**), 2.5 mol % $[(allyl)PdCl]_2$, LDA (1.5 equiv.), THF, RT.

c) Conjugate Addition.

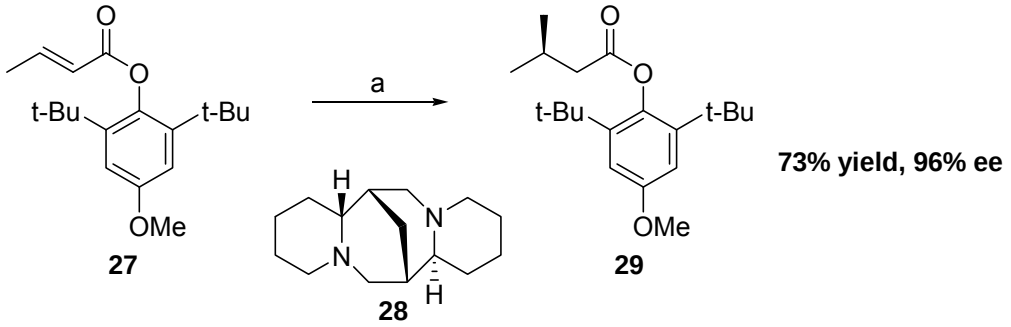


c) Et_3Al, CuTC, (S,R,R)-1 (**26**), Et_2O, -30°C.

Figure 6. Known C-C bond formation reactions that form an all-carbon quaternary stereocenter.[4]

1.2 ECAs to Enones.

Conjugate additions to enones are common reactions in many natural product syntheses.[19] Due to a large variety of donor and acceptor compounds that can be employed in this reaction, tremendous effort has been devoted over the last three decades to develop enantioselective asymmetric variants.[20] Copper mediated ECAs of organolithium and Grignard reagents to α,β-unsaturated systems covalently modified with chiral auxiliaries were the first successful approaches.[21] In addition, other preliminary methods utilized organocopper compounds with chiral nontransferable groups.[20,21] In 1997, the application of organolithium reagents in the presence of stoichiometric quantities of the chiral amine, (-)-sparteine **28**, was developed (Figure 7).



a) MeLi, (-)-sparteine (**28**), PhMe, -78°C

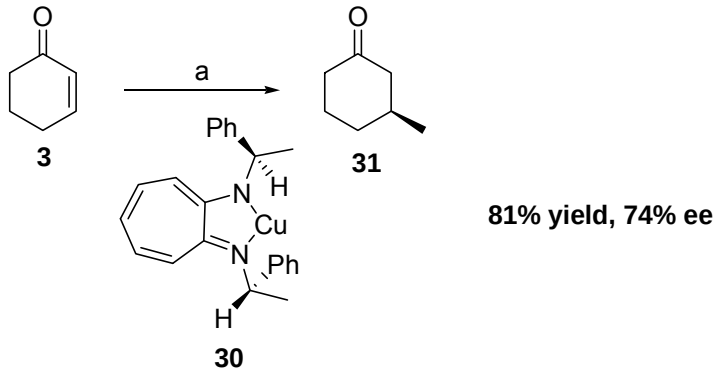
Figure 7. ECA with an organolithium reagent and a chiral amine.

ECAs of organolithium reagents to α,β-unsaturated systems possessing sterically crowded esters resulted in good yields (>70%) and high enantioselectivities (>90% ee).[22] Although the use of organolithium reagents produced practical results, the loading of chiral catalyst was large, (>10 mol %).

The high reactivity associated with organolithium reagents is a major problem in the development of catalytic asymmetric 1,4-addition reactions. The major problems faced with reactions using highly reactive organolithium reagents include a favoured 1,2-addition reaction and the co-existence of competing chiral and achiral 1,4-addition reactions. The development of an efficient chiral catalyst that avoids this regioselective preference is challenging. In order to overcome this

major regioselectivity problem, chemists have used large loading quantities of chiral catalysts, >10 mol %.[23]

The first reported ECA of a Grignard reagent to an enone, using catalytic quantities of a Cu-amide complex was performed by Lippard and coworkers in 1988 (Figure 8).[24]



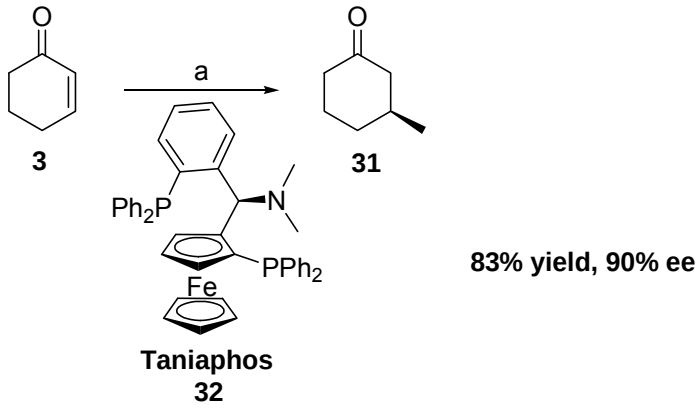
a) MeMgCl, H(CHIRAMT) (**30**), THF, -78°C

Figure 8. First ECA with a Grignard reagent and a Cu-amide complex.

Shortly following this influential work, diverse catalytic systems were developed based on copper thiolates[25-31] and monophosphine ligands.[32-35] However, the majority of these systems produced products with enantioselectivities seldom attaining 90% ee. Some exceptions include those of Tomioka[34] and Sammakia[35] where enantioselectivities of >92% ee were achieved for the addition of BuMgCl to cyclic enones. However, Tomioka used 32 mol% of a chiral amidophosphine and Sammakia used 12 mol% of a chiral ferrocenyl monophosphine in their additions to cyclic enones. Unfortunately, the loading of these chiral catalysts was still greater then the practical amount of <10 mol%.[36]

Grignard reagents have several limitations associated with the Cu-catalyzed conjugate addition. The problems faced with reactions using Grignard reagents in enantioselective reactions include: fast uncatalyzed side reactions, the existence of competing chiral and achiral copper complexes in solution and the usually detrimental effect of the presence of halides on enantioselectivity.[37] The nature of this halide effect is unknown; however, the use of alkylmagnesium chloride reagents have shown greater enantioselectivities then the use of alkylmagnesium iodide

reagents.[38] In 2004, Feringa found that Grignard reagents could be added to cyclic enones with high enantioselectivity (>95%) and regioselectivity with the use of commercially available bidentate ligands.[39] All other ECA ligands found in the literature functioned by means of a Cu catalyst and the use of a P, S, or Se with N or O donor atoms within the ligand structure. Usually the Cu catalyst is selectively coordinated to the Mg component of the organometallic species to fulfill the criteria of the conjugate addition.[40-42] Feringa notes that phosphoramidites ligands were initially tested but resulted in poor enantioselectivities.[43] In addition, Feringa observed that reactions with Grignard reagents in the presence of any free Cu salt in the system would result in an uncatalyzed reaction, even at -78°C. Therefore, Feringa proposed that a ligand that binds Cu ions tightly, such as a bidentate ligand, might be essential. Accordingly, the chiral ferrocenyl diphosphine ligand provided excellent stereocontrolled products in good yields >75%, despite the high reactivity of the Grignard reagents and the presence of halide ions (Figure 9). In addition, the ECA system using Taniaphos functioned with a moderate catalyst loading of 5 mol%.[39]



a) MeMgBr, Taniaphos (**32**), CuCl, Et_2O, 0°C.

Figure 9. Feringa's ECA with a Grignard reagent and Taniaphos.

Grignard reagents possessed such high reactivity that even in the presence of a chiral ligand, they often resulted in an undesired racemic reaction. As a result, chemists set out to explore the use of less reactive organometallic species, such as organo-zinc, copper, aluminum, silicon, or boron reagents, in combination with

different metal sources (Cu, Rh, Pd, Ni, Co). Dialkylzinc reagents were first employed by Alexakis in the mid-1990's (Figure 10)[10] and they have dominated the field of ECAs since.[44-49].

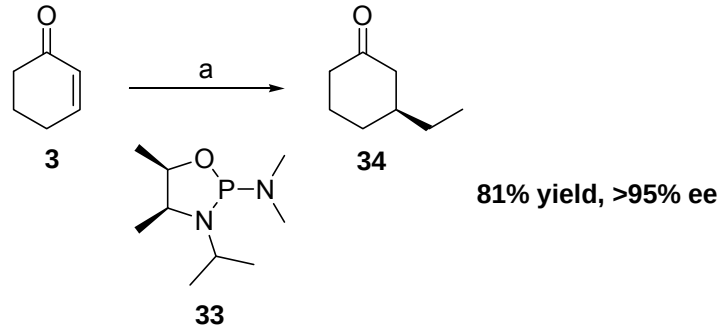


Figure 10. First ECA with a dialkylzinc reagent.

Dialkylzinc reagents possess many advantages because, compared with Grignard reagents, they demonstrate low reactivity in an uncatalyzed reaction and high tolerance for functional groups both in the substrate and the zinc reagent. Copper-catalyzed dialkylzinc additions have been useful in many reactions involving conjugated cyclic substrates such as cyclohexenones,[10] cyclopentenones,[11] unsaturated lactones[13] and lactams.[14] In addition, progress has been achieved with dialkylzinc reagents and challenging acyclic substrates such as chalcones,[12] benzylideneacetones,[50] aliphatic α,β-unsaturated ketones,[51] malonates[17] and nitroolefins.[15] Dialkylzinc reagents are compatible with a variety of functional groups.[52] As a result, the use of organozinc reagents eliminates other reactions such as 1,2-addition which is a problematic reaction with organomagnesium nucleophiles. Dialkylzinc reagents also have some disadvantages. For example, dialkylzinc reagents possess low atom efficiency, since the stoichiometry of the desired transfer ligand to zinc ratio is 2:1. In addition, dialkylzinc reagents are also much harder to synthesize and handle than reagents such as organomagnesium reagents.[53] The process of hydroboration alkyl-transfer permits the formation of functionalized organozinc reagents.[54]

Over the last decade, the reaction between dialkylzinc reagents and cyclic enones has been extensively studied.[44-49] Most studies of an ECA organozinc

reaction with cyclic enones were carried out in similar conditions. Typically, an organozinc ECA reaction is performed with diethylzinc and cyclohexenone in toluene in the presence of 0.5-5 mol% of a Cu salt and in the presence of 1-10 mol% of a chiral ligand. Fortunately, Cu-catalyzed organozinc reactions occur at a very slow rate in any solvent without the presence of a ligand.[55] Thus, the reaction is ligand-accelerated and adjusted according to the character of the chiral ligand. ECA organozinc reactions are carried out in solvents such as, PhMe, Et_2O, DCM, THF, EtOAc and ACN. Coordinating solvents usually result in the deceleration of the reaction.[36] High enantioselectivities have been obtained using all solvents.

The copper salt is essential for high catalytic activity and high enantioselectivity. Both Cu^{+1} and Cu^{+2} salts have been used successfully. The most widely used copper salt has been Cu^{+1} triflate, however, its demonstrated catalytic activity was equal to that of Cu^{+2} triflate. Cu^{+2} triflate is the preferred Cu salt as it is easily handled in open air, whereas, Cu^{+1} triflate is very sensitive to oxidation and should be handled with care.[56] The equal catalytic activity of the two Cu triflate species is explained by the fact that Cu^{+2} salt is reduced in situ to the Cu^{+1} salt, which is the true catalytic species. The Cu^{+2} triflate's higher catalytic activity over copper halides is thought to be explained by the enhanced Lewis acidity of triflate Cu salts.[57] On the other hand, the high efficiency in catalytic activity of copper carboxylates salts was explained by their lipophilicity or solubility in a non-polar solvent. The best enantioselectivities using Cu carboxylates were found with copper thiophene-2-carboxylate, CuTC.[36]

The chiral ligand is the centerpiece of this reaction as it increases the rate and produces an enantioselective reaction. The level of enantioselectivity is entirely due to its presence. The main type of ligand and most successful associated with organozinc reagents is the family of chiral phosphorus-based ligands. Other ligands include sulfonamides and bis(oxazolines), but they have been much less studied. Sources of trivalent phosphorus ligands, such as phosphanes, phosphites, phosphoramidites and phosphonites, have shown to strongly accelerate organozinc ECA reactions.[55] Most phosphorus ligands commonly exist as monodentate or bidentate type structures. During a typical organozinc ECA, two equivalents of

ligand are required per Cu ion.[10] As shown for the catalytic cycle in Figure 11, the first equivalent of phosphorus ligand is required to guide the reaction and the second equivalent is replaced by π complexation of the selected enone to the Cu species.[58-61] The accepted mechanism of ECA with the use of organozinc reagents is understood to follow a pathway where there is an oxidative addition to a Cu^{+3} intermediate, followed by reductive elimination.[62]

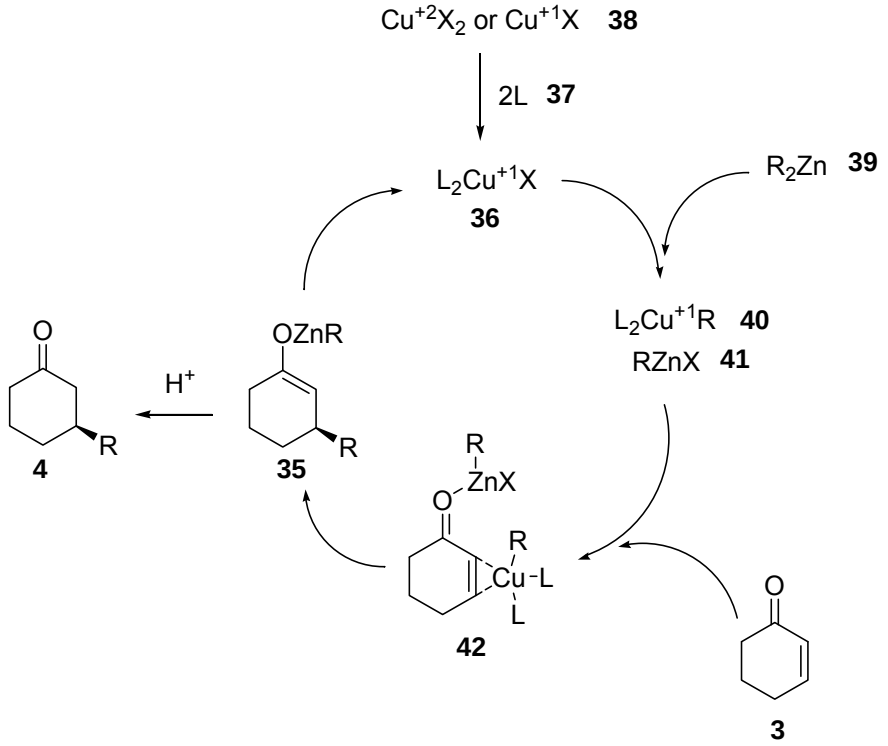


Figure 11. Mechanistic pathway of an ECA with dialkylzinc reagents.[62]

To date, the most studied ligands are those bearing three heteroatoms around the phosphorus atom: phosphites and phosphoramidites (Figure 12). These phosphites and phosphoramidites usually possess a phosphorus atom incorporated in a ring formed from a diol or an amino alcohol. The chirality of these ligands originates from the diol unit, the exocyclic unit, or both. These types of ligands can also be associated with a matched or mismatched relationship where dissimilar catalytic behaviour can occur for each of the synthetically possible diastereomeric ligands. TADDOL ligands **45** are composed of a phosphorus atom in a seven-membered ring. Several ECAs incorporating this type of ligand have been

synthesized and tested.[58,63,64] In addition, this type of ligand can exist in two forms, those that possess an exocyclic chiral group and those that do not. However, the absence of an exocyclic chiral moiety, results in low to moderate enantioselectivity on enones.[58] Binaphthol-based ligands **47** are the most studied subclass of the phosphite and phosphoramidite ligand family. The most successful ligands of this subclass are those bearing a chiral exocyclic moiety, such as an alcohol for phosphites or an amine for phosphoramidites.[65] Similar to the TADDOL ligand class, binaphtol-based ligand diastereomers also have matched or mismatched relationships. Non-phosphorus ligands have rarely been utilized with dialkylzinc reagents. However, sulfonamides,[66] diaminocarbenes,[67] modified binaphthols,[68-70] sugar-derived ligands,[71] thiazolidines[72] and oxazolines[73] have been shown to accelerate the conjugate addition of dialkylzinc. Non-phosphorus ligands have a tendency to promote an efficient reaction with 2-cyclohexenone, but they work poorly with other enones.[74]

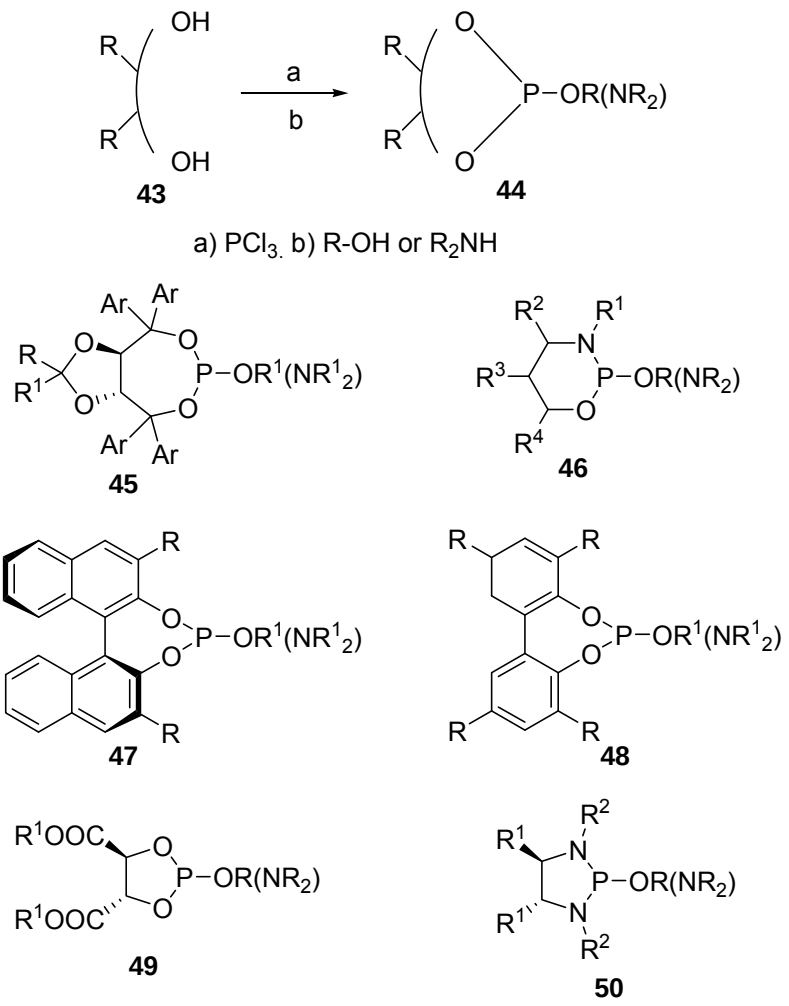
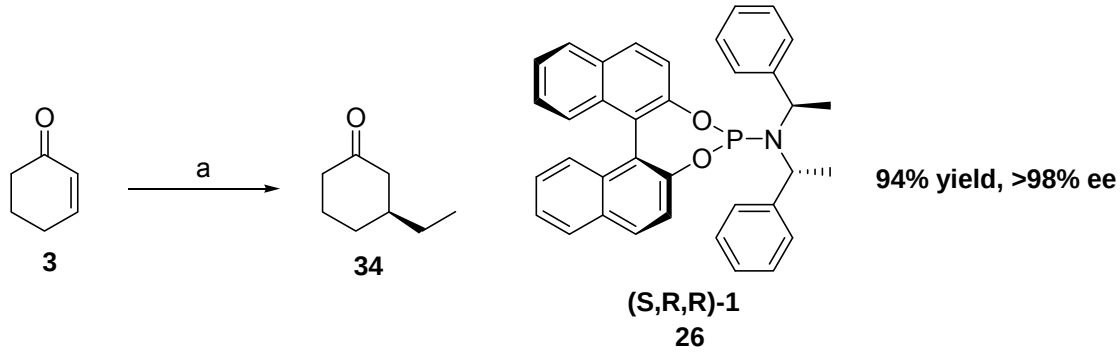


Figure 12. Phosphites and phosphoramidites backbone structures.

The most widely studied substrate for organozinc ECAs has been 2-cyclohexen-1-one (**3**). Cyclohexenone is a very reactive species and, in most articles, it is the only enone screened against several ligands. The cyclic structure of cyclohexenone avoids the problem of conformer interconversion. In 1997, Feringa[75] reported that successful ECAs were obtained using a $Cu(OTf)_2$ phosphoramidite ligand system in combination with dialkylzinc reagents and cyclohexenone **3** (Figure 13).



a) Et_2Zn, $Cu(OTf)_2$, (S,R,R)-1 (**26**), PhMe, -30°C.

Figure 13. Feringa's ECA to 2-cyclohexen-1-one.

The reaction between Et_2Zn, compound **3** and the catalyst prepared from $Cu(OTf)_2$, (2 mol%) and **26** (4 mol%) provided **34** in 94% yield and an ee value greater than 98%. Excellent yields and enantiomeric excesses ranging from 94% to greater than 98% were obtained for cyclohexenone with a variety of zinc reagents. The high stereocontrol observed in the formation of a number of 3-alkyl cyclohexanones (R = Me, Et, *i*-Pr) led Feringa to examine catalytic 1,4-additions of diheptyl zinc and functionalized dialkylzinc reagents. Although the yields of the reactions were diminished slightly as the size of the alkylzinc reagent increased, the enantiomeric excesses achieved were >90%. Feringa noted that the phosphoramidite catalyst also tolerated ester and acetal functionalities. Based on a crystal structure of the phosphoramidite catalyst, Feringa proposed a transition state (Figure 14). It consists of a copper atom bonded to two phosphoramidite ligands and to an ethyl group from the zinc reagent. In addition, the copper atom is coordinated to the enone functionality of the cyclohexenone substrate.

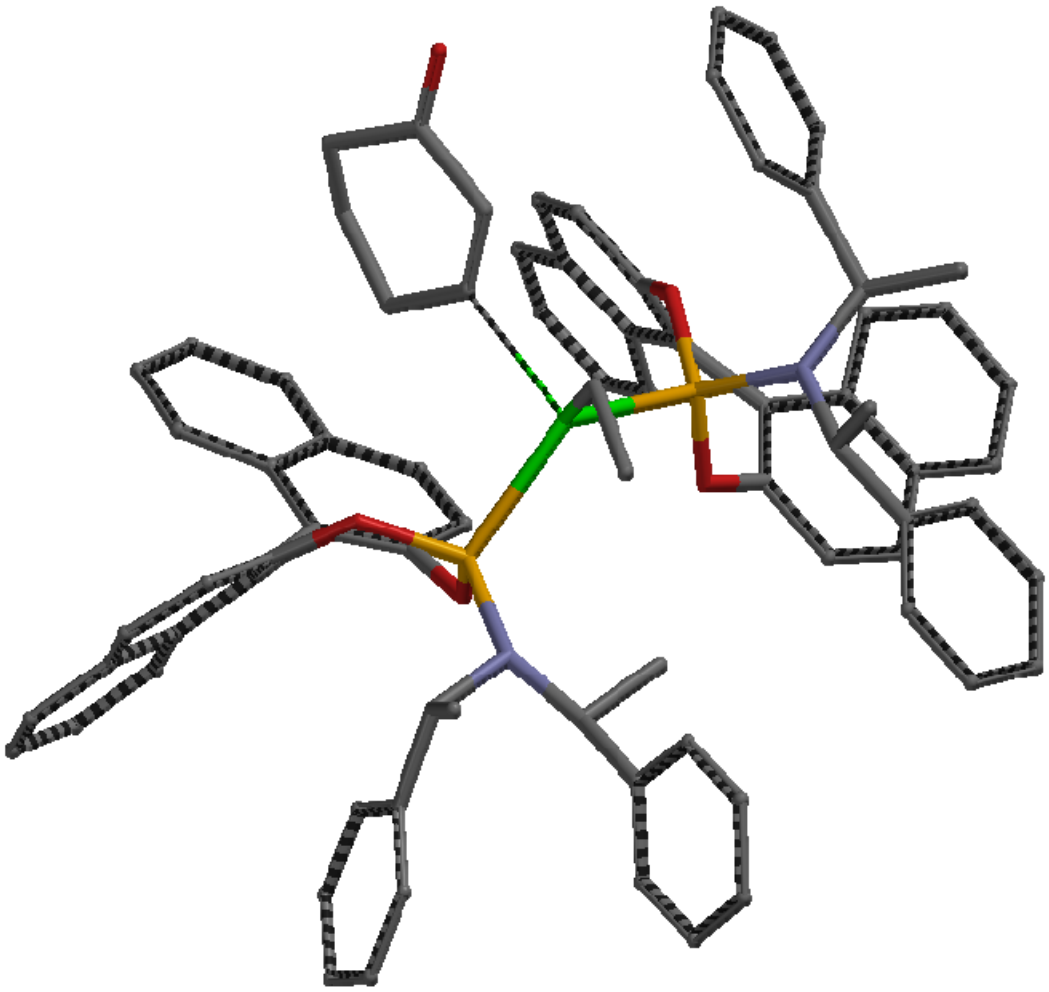


Figure 14. Cu-Phosphoramidite Ligand Transition State Proposed by Feringa.[75]

Methods using metals other then copper have also been developed. ECAs to enones using alkenylboronic acids and chiral rhodium catalysts have produced products with high yields and enantioselectivities. The activation in these types of reactions[76] is thought to occur by means of transmetalation to a chiral alkenylrhodium species (Figure 15).

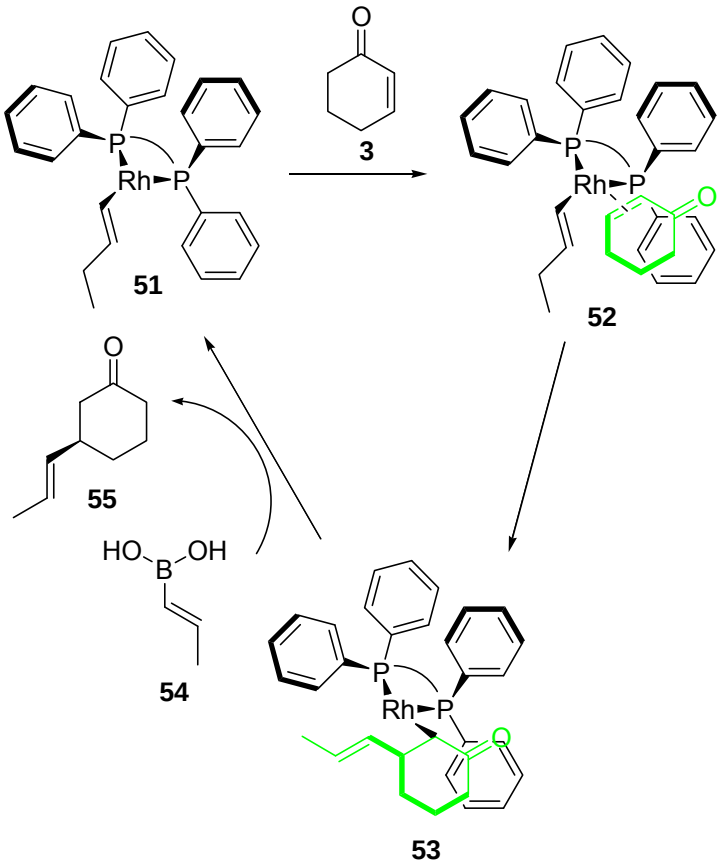
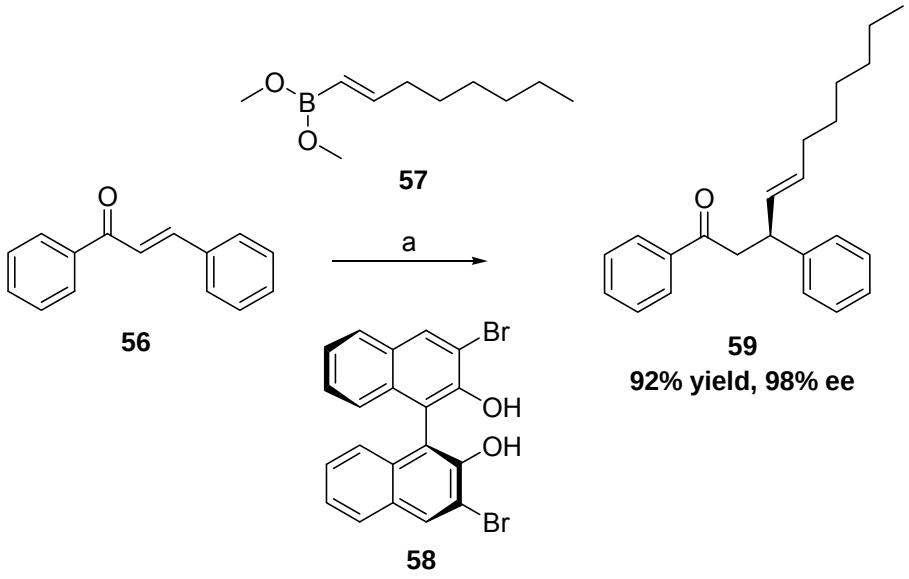


Figure 15. Transmetalation to a chiral alkenylrhodium species.

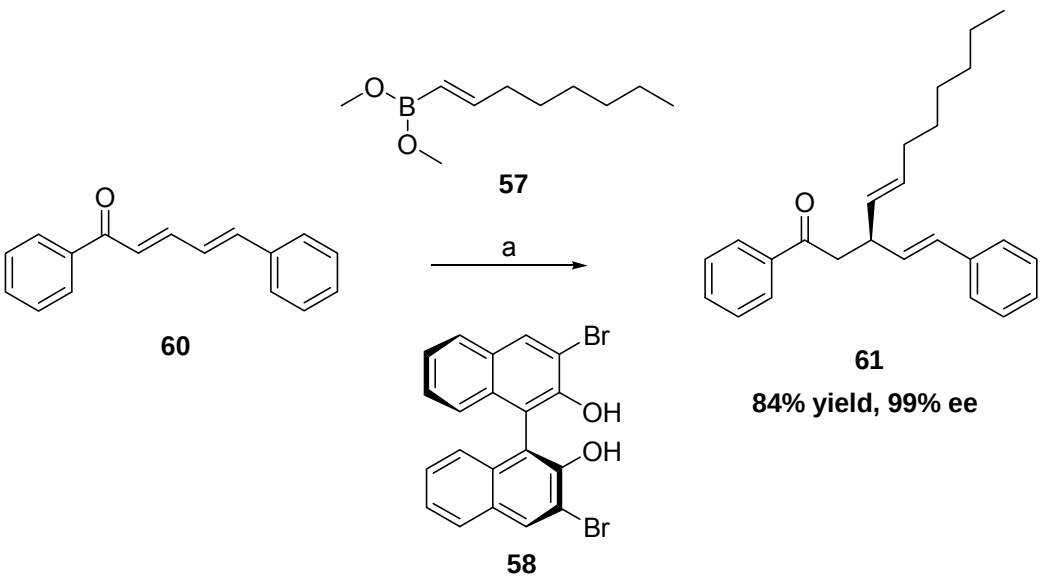
Recently, Chong[77] demonstrated that esterification of boronic acids with suitable chiral diols could be utilized as an alternative method of activation. It was hypothesized that a chiral diol could be turned over during the reaction and the reaction mechanism would not involve a transition metal catalyst. Chong found that a 1,4-alkenylation of chalcone **56** using a boronate **57** could be achieved using catalytic amounts of binaphthol **58** (Figure 16).



a) (**57**), (**58**), CH_2Cl_2, 4A MS, 40°C.

Figure 16. Chong's 1,4-alkenylation of chalcone.

Many binaphthols were examined and were all able to catalyze the addition to produce **59** with high enantioselectivity. The reaction proceeded with as little as 3 mol% of catalyst with no decrease in yield or enantioselectivity. Chong further investigated this reaction with other enones where the phenyl groups of **56** were exchanged for other functionalities. Again, this reaction demonstrated high selectivities for virtually all the enones tested. Highest selectivities, >99% ee, were observed for enones substituted at the β-position with relatively large aryl groups. Conjugated dienones, where the phenyl group at the β-position was replaced by CH=CHPh **60** (Figure 17) or CMe=CHPh, also produced 1,4-addition products with high selectivities, 99% ee.



a) (**57**), (**58**), CH_2Cl_2, 4A MS, 40°C.

Figure 17. Chong's 1,4-alkenylation of the conjugated dienone **60**.

Enones where the phenyl group at the β-position was replaced with different alkyl groups produced high selectivities, >94% ee, regardless of whether the group was a methyl, *n*-alkyl, or branched. Lastly, an enone where the phenyl group at the β-position was replaced by a carbomethoxy group reacted to produce high selectivity, >96% ee. The high selectivities of these reactions led Chong to suggest a possible favoured transition state demonstrating the link between the boronic acid-chiral diol complex and the enone substrate (Figure 18).

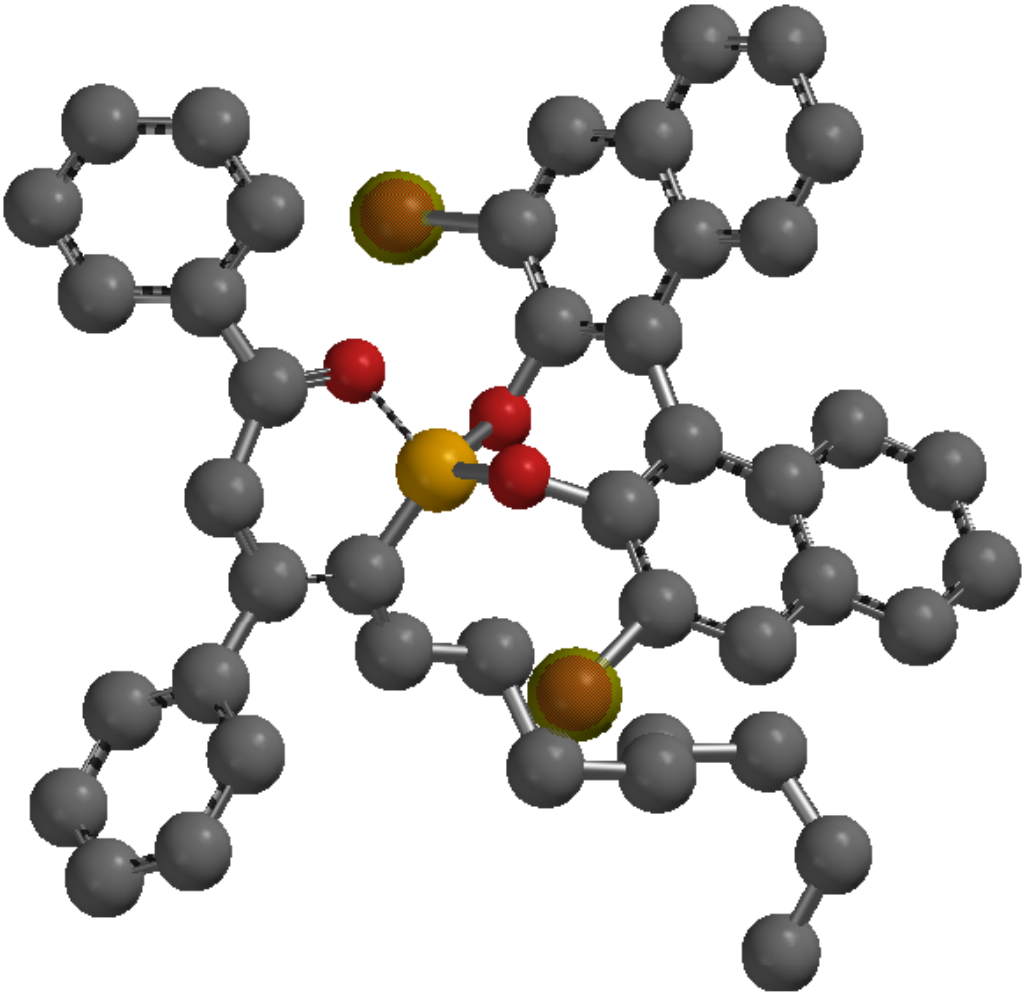


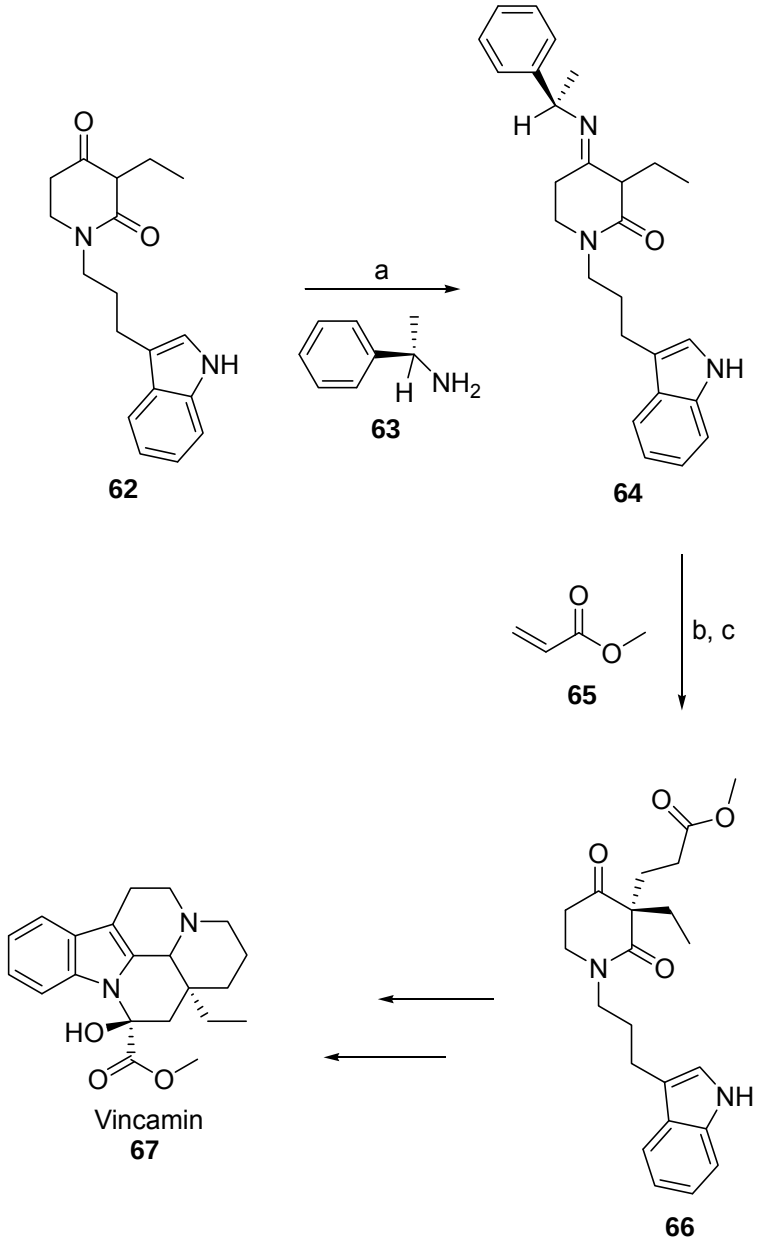
Figure 18. Chong's 1,4-alkenylation favoured transition state.

Chong discovered the first example of ECA alkenylation methodology that does not rely on transition metals.

1.3 Diastereoselective Conjugate Addition (DCA) to Enones.

Chiral auxiliaries are extremely versatile synthetic components for DCA reactions.[78] As a result, the product formed from a DCA reaction can then be converted into an enantioenriched product by the removal of the chiral auxiliary. D'Angelo first reported the use (*R*)-1-phenylethylamine a chiral auxiliary in an intermediate step in the total synthesis of (+)-vincamin **67**.[79] The intermediate **64**

was prepared by converting lactam **62** at elevated temperature with (*R*)-1-phenylethylamine (**63**) and with two equivalents of methyl acrylate (**65**) to yield the conjugate addition product in 70% yield and 92% ee after cleavage of the auxiliary (Figure 19).

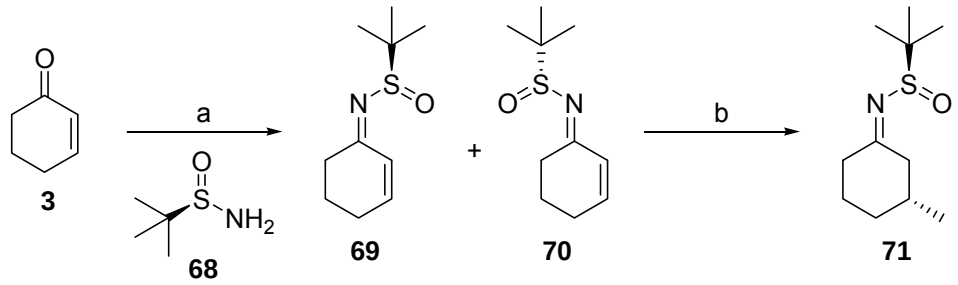


a) (**61**), PhMe, Reflux. b) (**65**), 60°C. c) AcOH, H_2O.

Figure 19. DCA in the synthesis of (+)-vincamin.

The auxiliaries utilized in these types of reactions are readily condensed with the ketone and can be recovered almost quantitatively after workup.

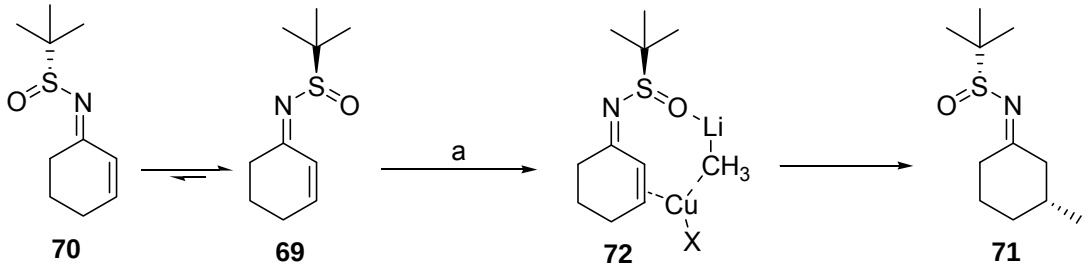
Sulfinyl imines are a special class of imines that display unique reactivity and stereoselectivity due to the presence of the stereogenic and electron withdrawing nitrogen-sulfinyl group.[76] N-*tert*-Butanesulfinyl imines are members of the class that are exceptionally versatile synthetic intermediates. N-*tert*-Butanesulfinyl imines are readily prepared by condensation of *tert*-butanesulfinamide with aldehydes or ketones. Diastereoselective addition of diverse nucleophiles followed by acidic removal of the sulfinyl group efficiently provides enantioenriched amine or ketone products.[80,81] Lately, the Ellman group has embarked on an effort to access more complex amine products with multiple stereocenters by first performing diastereoselective transformations on starting N-tert-butanesulfinyl imines to provide more complex imine intermediates that could be subsequently converted to enantioenriched amine products (Figure 20).[82]



a) $Ti(OEt)_4$, (**68**), THF, Reflux. b) CuX, MeLi, Et_2O, -78°C.

Figure 20. Ellman's DCA via the formation of a sulfinyl imine intermediate.

The α,β-unsaturated *tert*-butanesulfinyl ketimines **69** and **70** were produced in good yield, however, a 2:1 mixture of E/Z isomers was observed. Ellman also observed that following the ECA the diastereoselectivity of the product **71** greatly exceeded the modest E/Z isomer ratio. This, in turn, suggested that one of the imine isomers reacted preferentially with the cuprate concomitant with a rapid imine isomer equilibration (Figure 21). Ellman suggested that the chiral sulfinyl imine functionality directly assisted the alkyllithium addition through a cyclic transition state as in **72** (Figure 22).



a) CuX, MeLi, Et_2O, -78°C.

Figure 21. Ellman's suggested reaction pathway.

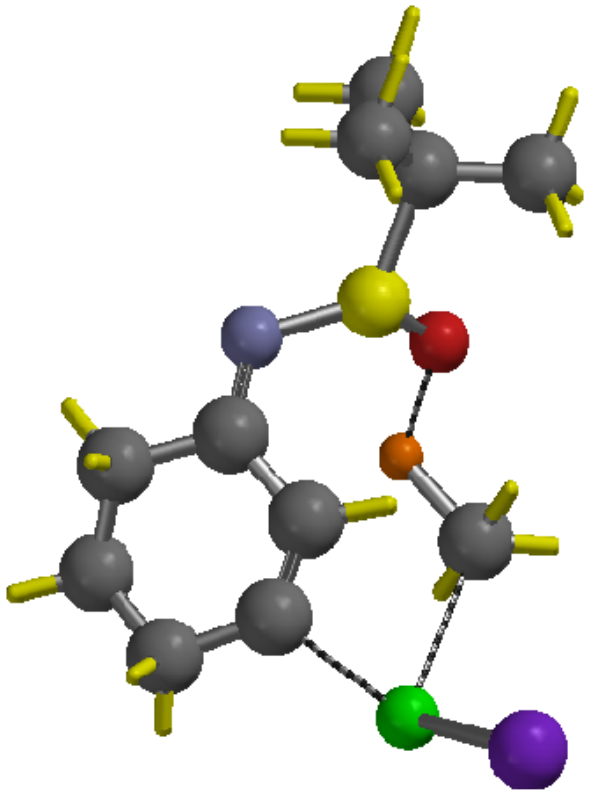
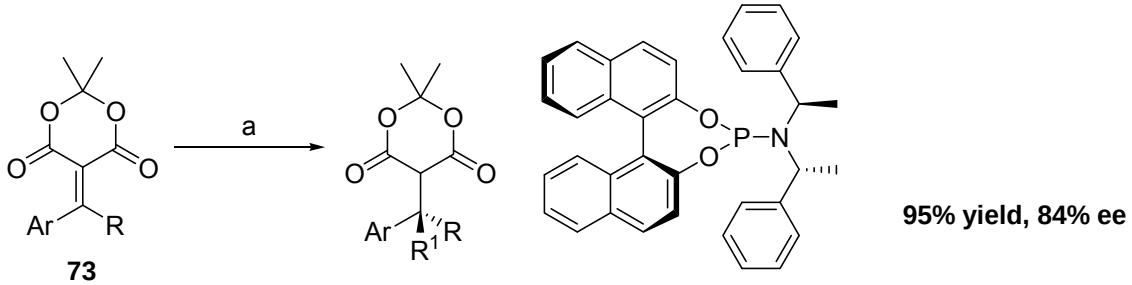


Figure 22. Ellman's suggested sulfinyl imine intermediate.

The type of cuprate also seemed to play an important role as diastereomeric ratios varied depending on the copper source. These first examples of ECAs to α,β-unsaturated tert-butanesulfinyl ketimines provided insights that sulfinyl imines could be potentially useful intermediates in the asymmetric synthesis of a variety of natural products.[82]

1.4 ECAs to β,β-Disubstituted Enones.

Conjugate addition[75] of carbon nucleophiles to β,β-disubstituted enones or electron-deficient olefins is a strategy used to create all-carbon quaternary stereocenters.[48] There are only a few literature examples of creating all-carbon quaternary stereocenters and this may be credited to the inherent poor reactivity of β,β-disubstituted alkene acceptors.[1] In 2006 Fillion[83] reported an asymmetric synthesis of all-carbon benzylic quaternary stereocenters. These quaternary stereocenters were formed through Cu-catalyzed addition of dialkylzinc reagents to 5-1-arylalkylidene or Meldrum's acids in the presence of a phosphoramidite ligand (Figure 23).



a) $R^1{}_2Zn$, $Cu(OTf)_2$, (S,R,R)-1 (**26**), DME, -40°C to RT.

Figure 23. Fillion's synthesis of all-carbon benzylic quaternary stereocenters.

The asymmetric synthesis of ECA reactions with Meldrum's acids to produce all-carbon stereocenter derivatives resulted in excellent conversions (95%) and good enantioselectivities (>70% ee). It was also noted that enhanced enantioselectivity occurred with the introduction of a halogen group in the para position of the aromatic ring. A variety of dialkylzinc reagents, Et_2Zn, Me_2Zn, *i*-Pr_2Zn and *n*-Bu_2Zn were utilized to react with **73**. With the exception of *i*-Pr_2Zn resulting in a low enantioselectivity, the remaining alkylzinc reagents resulted in excellent enantioselectivities (90-95% ee). This method described was the first highly enantioselective synthesis of all-carbon benzylic quaternary stereocenters via an

ECA of dialkylzinc reagents to an acyclic site of Meldrum's acids in the presence of a phosphoramidite ligand.

In 2007, Hoveyda[84] reported the design of a new chiral N-heterocyclic carbene (NHC) ligand that could be used for ECA synthesis of all-carbon quaternary stereogenic centers to cyclic β-keto esters with the use of organozinc reagents (Figure 24).

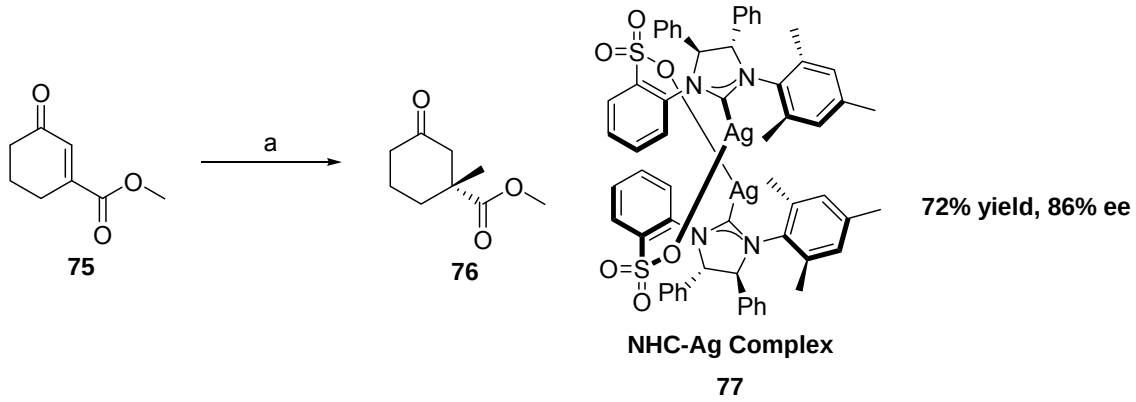
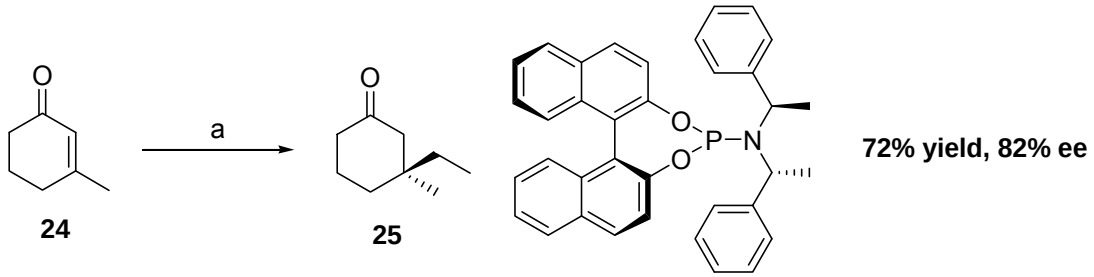


Figure 24. Hoveyda's ECA construction of a quaternary stereogenic center.

This investigation examined the ability of Cu complexes generated from the reaction of **77** and $Cu(OTf)_2 \cdot C_6H_6$ to support an ECA of Me_2Zn to six-membered ring β-keto esters **75**. Hoveyda observed that a sulfonate-containing chiral NHC promoted the addition of Me_2Zn to a six-membered ring β-keto ester **75** with significantly higher efficiency (>98% conversion) and superior enantioselectivity (>80% ee) than with previous NHC ligands.[84] Hoveyda did not make any mention of how this reaction proceeded. However, Hoveyda did state that the steric and electronic attributes of these ligands must have assisted these catalytic reactions by producing higher reactivities and selectivities.

In 2005, Alexakis[4] reported the first successful example of constructing an all-carbon quaternary stereocenter within a cyclic enone. An ECA was performed to 3-substituted cyclohexenones in the presence of phosphoramidite ligands (Figure 25).



a) Et_3Al, CuTC, (S,R,R)-1 (**26**), Et_2O, -30°C.

Figure 25. First ECA to a cyclic enone to form an all-carbon stereocenter.

Alexakis first acknowledged that Cu-catalyzed ECAs of organozinc reagents had been successfully applied to many β-substituted substrates. However, he also added that ECA reactions with organozinc reagents and β,β-disubstituted substrates failed, perhaps resulting from some steric reasons. As a result, Alexakis changed from zinc to aluminum reagents. Trialkyaluminum reagents have been known to react with α,β-unsaturated cyclic[85] and acyclic enones[86] and nitro olefins.[87] Furthermore, Alexakis used the rationale that the stronger Lewis acidity of Al would create a better activation of the β,β-disubstituted substrate than Zn, thus overcoming the inherent steric hindrance.[4] The mechanism of ECA reactions with the use of alkylaluminum reagents was thought to follow a similar mechanistic pathway to that of dialkylzinc reagents (Figure 26).[88]

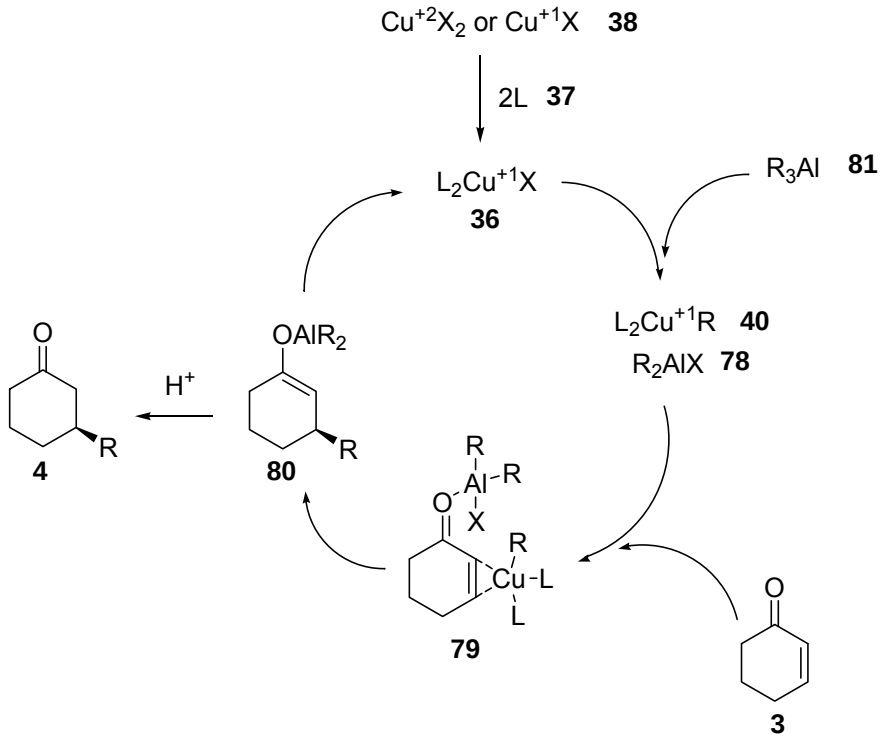


Figure 26. Mechanistic pathway of an ECA with alkylaluminum reagents.

1.5 ECAs to Dienones.

The chemistry of dienones is known to be similar to that of masked *p*-quinols and includes many reactions, such as 1,2-addition reactions to the carbonyl functionality, as well as 1,4-addition and annulation reactions of the enone functionality. The synthetic utility of all of these reactions is limited by the tendency of dienones to aromatize. Dienones can aromatize through the dienone-phenol rearrangement in acidic conditions. As shown in Figure 27, the dienone-phenol rearrangement of unsymmetrical cyclohexa-2,5-dienones can lead to four potential aromatic products.[6]

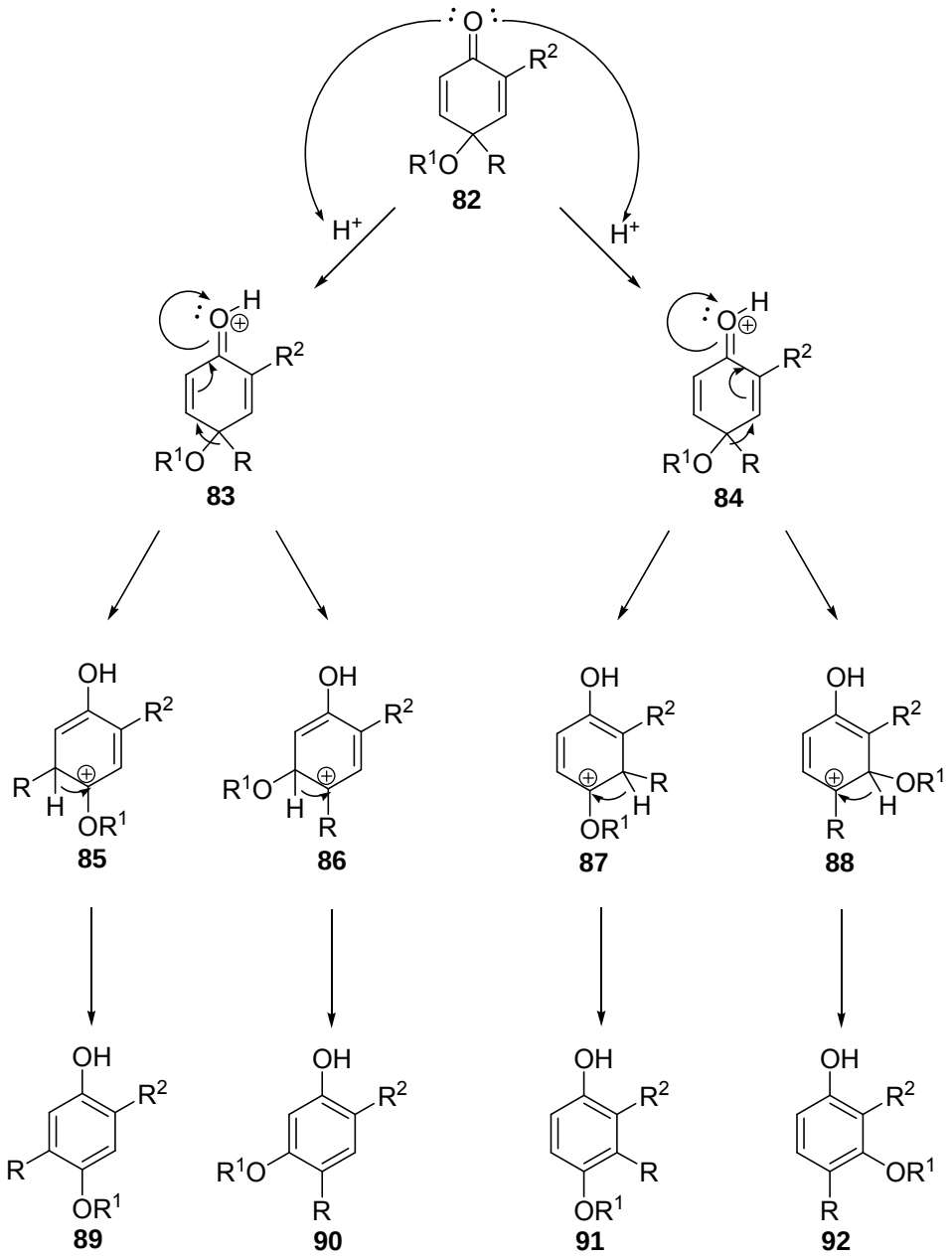
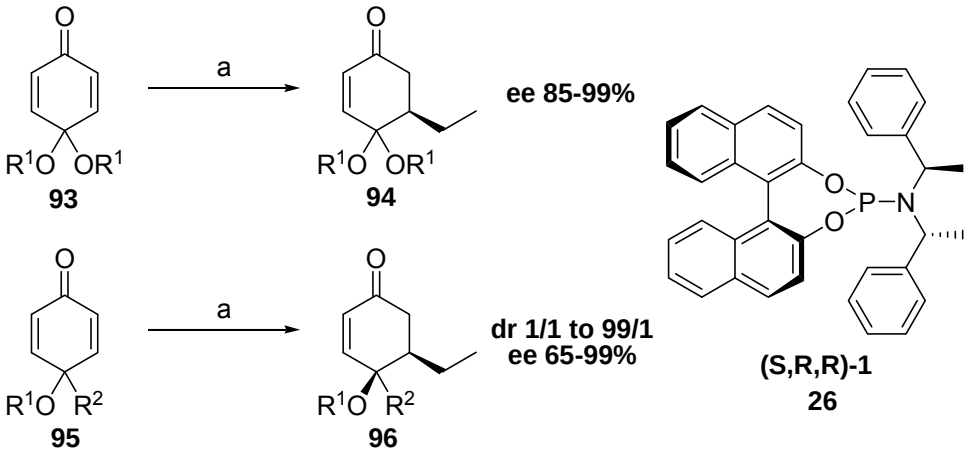


Figure 27. Dienone-phenol rearrangement pathways.[6]

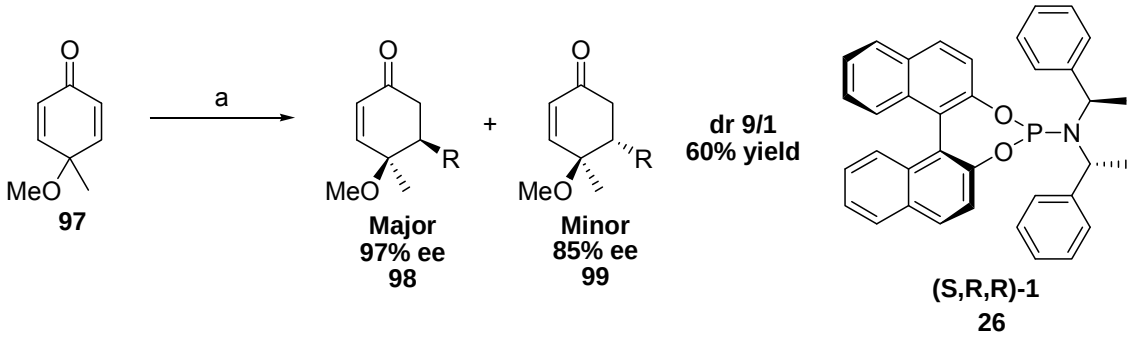
Although dienones undergo rearrangements easily under acidic conditions, dienones such as substituted cyclohexadienones have been shown to react smoothly with dialkylzinc reagents to produce high enantioselectivities. Feringa[89] reported that successful ECAs were obtained using a $Cu(OTf)_2$ phosphoramidite ligand system in combination with dialkylzinc reagents and several symmetric 4,4-disubstituted cyclohexadienones (Figure 28).



a) Et_2Zn, $Cu(OTf)_2$, (S,R,R)-1 (**26**), PhMe, -30°C.

Figure 28. Feringa's ECAs to 4,4-disubstituted cyclohexadienones.

Using a phosphoramidite ligand **26**, ECAs to the cyclohexadienone **97** possessing a MeO and a Me substituent at the 4 position produced the formation of two diastereoisomers **98** and **99**. The diastereomeric ratio was 9/1, and the enantiomeric excess of the major and minor products were 97% and 85%, respectively (Figure 29). Feringa noted that the basis of the observed diastereoselectivity may be a result of a steric or syn coordination effect from the oxygen atom of the alkoxy moiety to the catalytic species.



a) R_2Zn, $Cu(OTf)_2$, (S,R,R)-1 (**26**), PhMe, -30°C.

Figure 29. Feringa's diastereoselective ECA.

In addition, it was also noted that if the Me substituent of **97** were replaced with a much larger benzyl group, the diastereomeric ratio of **98** and **99** was increased to

97/3 and the enantioselectivity remained excellent (93% ee) for the major diastereoisomer. Feringa demonstrated that a copper-phosphoramidite chiral catalyst reacted with 4,4-disubstituted enones to produce ECA products with excellent stereoselectivity. As a result, a new catalytic method was discovered in order to synthesize several multifunctional cyclohexenones with high diastereoselectivity and high enantioselectivity.

In 1996, Carreno[90] investigated the behavior of the chiral dienone **100** upon reaction with organoaluminum reagents. The chiral dienone **100** possessed a chiral sulfoxide moiety as well as a hydroxyl moiety at the γ position of the carbonyl (Figure 30).

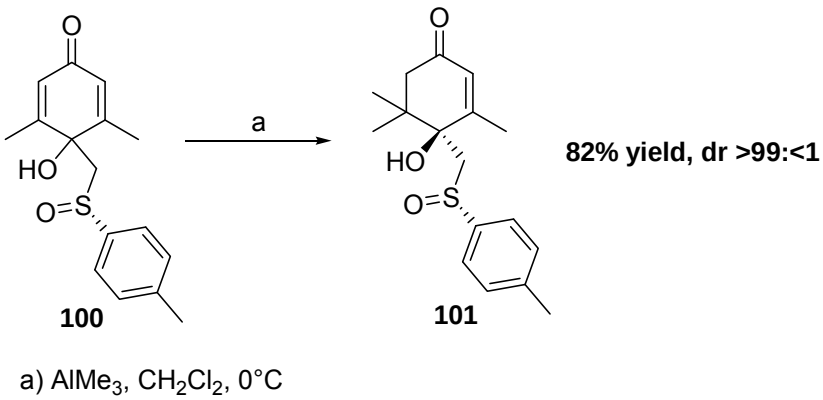


Figure 30. Carreno's 1,4-addition to **100**.

Carreno found that a 1,4-addition proceeded to **100** without other metal catalysts in good yields and mild conditions. Carreno also observed a similar result to that of Feringa and Ellman where there was a coordination effect from the oxygen atom. In this case, a crystal structure determined that the reaction took place on the same face as the hydroxyl moiety. As a result, total facial diastereoselectivity and an effective desymmetrization of the dienone moiety were achieved. Carreno also observed that when the free hydroxyl moiety was protected or the sulfoxide moiety was absent, a 1,4-addition using an organoaluminum reagent did not proceed. Carreno explains this 1,4-addition reaction where **100** proceeds through a chair-like transition state where the hydroxyl and sulfoxide moieties assist the aluminum species to perform the addition (Figure 31).

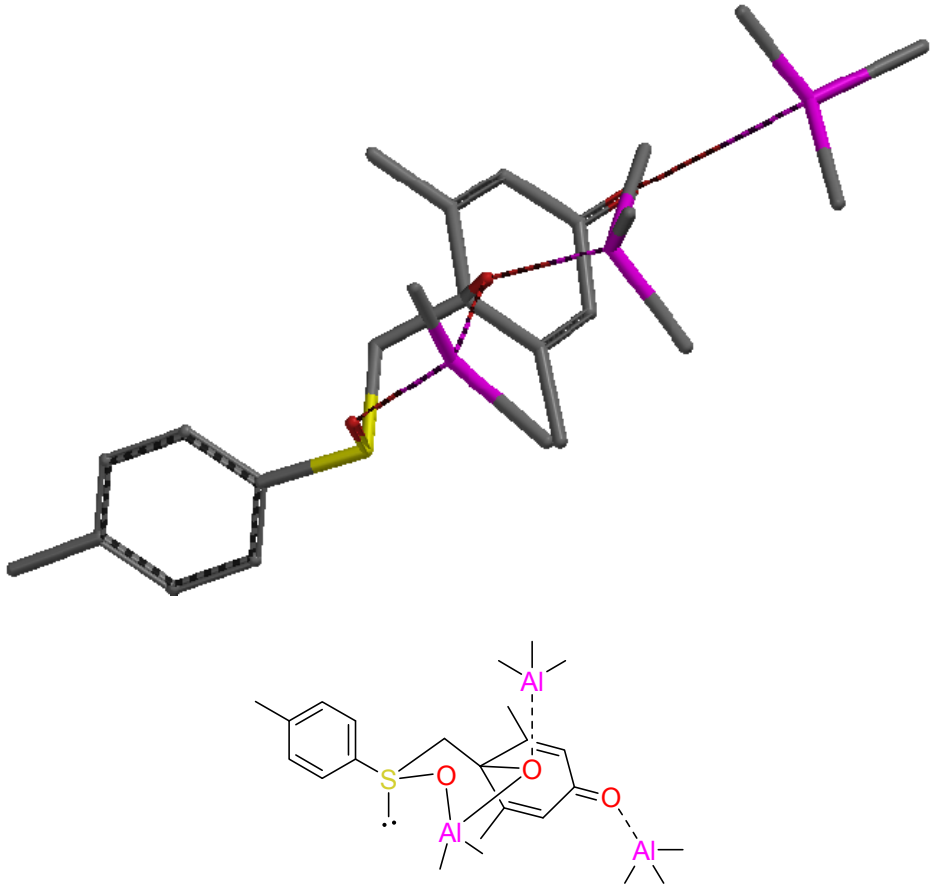
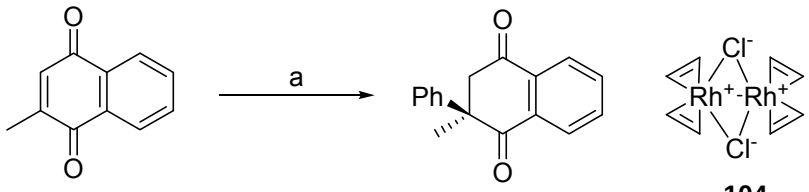


Figure 31. Formation of a chair-like conformation between **100** and Me_3Al.

Another recent communication by Hayashi[91] reported the development of a rhodium-catalyzed ECA of arylboronic acids to 2-methyl-1,4-naphthoquinone providing a 1,4 addition product in moderate yield (70%) and in high enantioselectivity (>99% ee) (Figure 32).



102 **103** **104**

a) $PhB(OH)_2$, (R)-binap, (**104**), KOH, Dioxane/H_2O, 50°C.

Figure 32. Hayashi's ECA construction of a quaternary stereogenic center.

Hayashi discovered a new method to perform an ECA to an α,β-unsaturated β,β-disubstituted cyclic enone via a rhodium-binap catalyst and the use of boronic acids. The faces of enone **102** were differentiated by the Rh-binap catalyst. Hayashi attempted to explain the observed regioselectivity in these ECAs of arylboronic acids to 2-methyl-1,4-naphthoquinone proposing a transition state where there was an extreme steric repulsion between the methyl substituent of **102** and the phenyl group of the catalyst in the transition state (Figure 33).

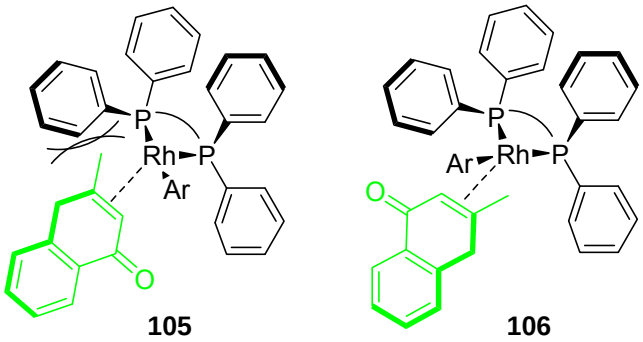


Figure 33. Hayashi's sterically hindered **105** and less hindered **106** transition states.

1.6 Cyclohexadienones Ketals

Cyclohexadienone ketals are potentially useful building blocks for natural product synthesis. So far, four types of cyclohexadienones have proven to be useful in the synthesis of racemic compounds (Figure 34).[2]

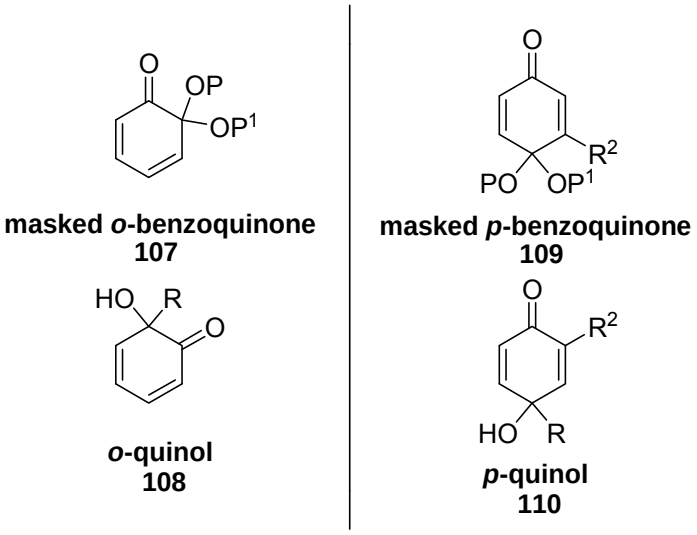
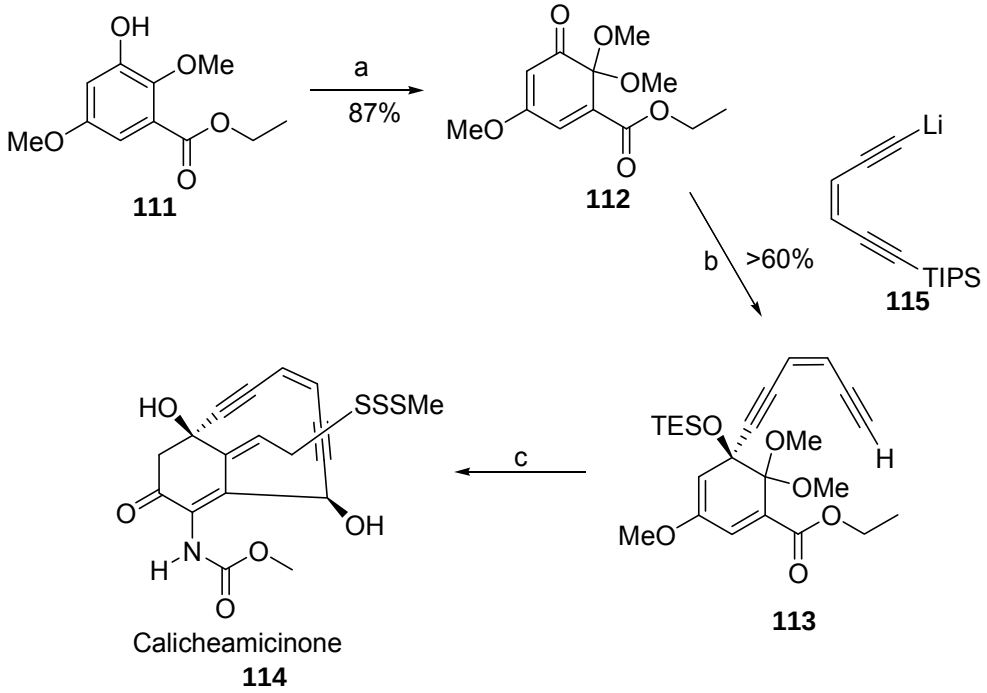


Figure 34. Four types of potentially useful chiral cyclohexadienone substrates.[3]

The masked *o*-benzoquinone substrate has played a key role in the early steps of the synthesis of calicheamicinone, a precursor in the synthesis of the antitumor antibiotic calicheamicin[92] (Figure 35).

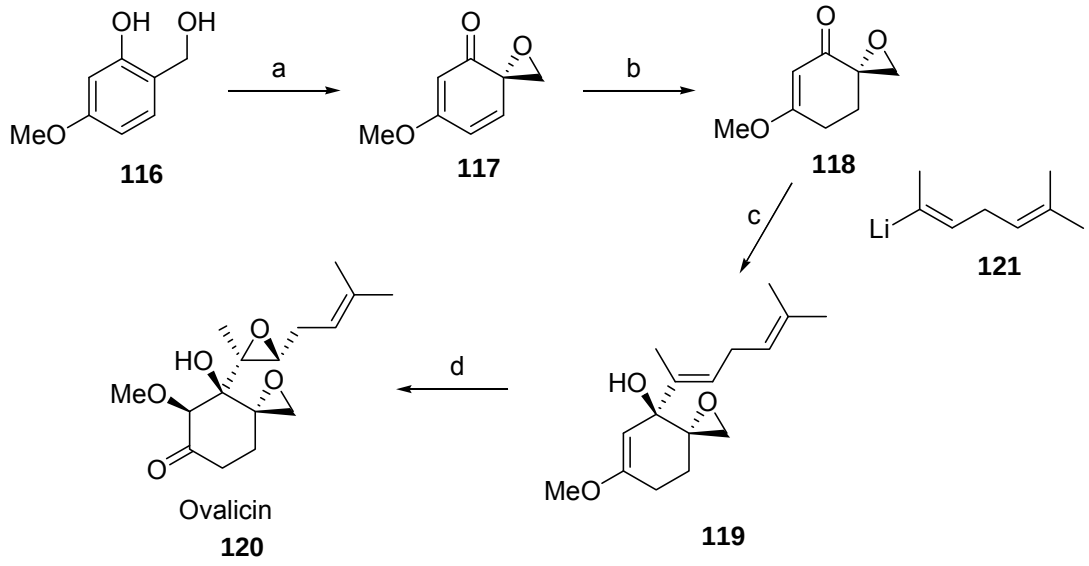


a) PIDA, MeOH. b) (**115**), TBAF, TESCl. c) Several additional steps.

Figure 35. Preliminary steps in the synthesis of calicheamicinone.

Magnus[93] reports the use of a masked *o*-benzoquinone core in the synthesis of calicheamicinone **114**. The reaction of phenol **111** with PIDA in MeOH affords the dimethoxy *o*-benzoquinone ketal **112**. Next, the 1,2-addition of a lithium acetylide **115** to the ketone functionality of **112** followed by TBAF deprotection of the acetylene and protection of the resulting tertiary alcohol as the TES siloxy ether affords **113** in >60% overall yield. Then, after several additional steps, this intermediate **113** can be converted into calicheamicinone **114**.

The second substrate of the cyclohexadienone family is the class of *o*-quinols. *O*-quinols have also been used to synthesize antibiotic and antitumor natural products. For example, Corey's[94] beginning steps during the synthesis of ovalicin, an antibiotic isolated from *Pseudorotium ovalis* cultures, demonstrated the utilization of this type of starting substrate (Figure 36).



a) $NaIO_4$. b) Diimide. c) (**121**). d) Several additional steps.

Figure 36. Preliminary steps in the synthesis of Ovalicin.

Corey demonstrated that subjecting compound **116** to $NaIO_4$ generates the spirocyclohexadienone **117** in a 61% yield. Next, the reduction of **117** with diimide affords the desired epoxide **118** in 77% yield. Next, the 1,2-addition of an unusual vinyllithium reagent **121** to the carbonyl group occurs in a diastereoselective

fashion, results in **119**. Lastly, subsequent functional group manipulations provide ovalicin **120**.

Of the four types of cyclohexadienones that contain a heteroatom at the sp^3-hybridized site within the six-membered ring system, the masked *p*-benzoquinone ketal is the best studied and most exploited.[2] The masked *p*-benzoquinone ketal has served as the key building block in the total syntheses of five major natural product families: the munumycins[95], huperzines[96], torreyanoids[97], diepoxins[98] and illudines[99] (Figure 37).

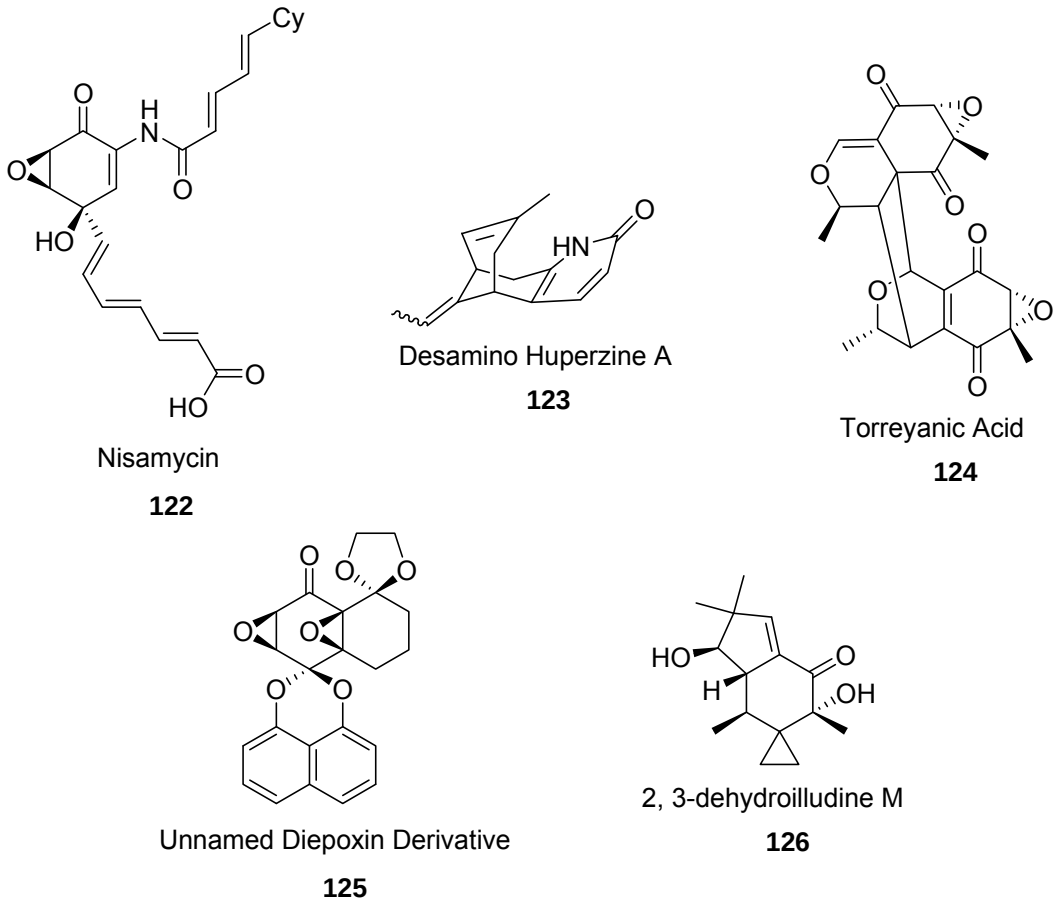
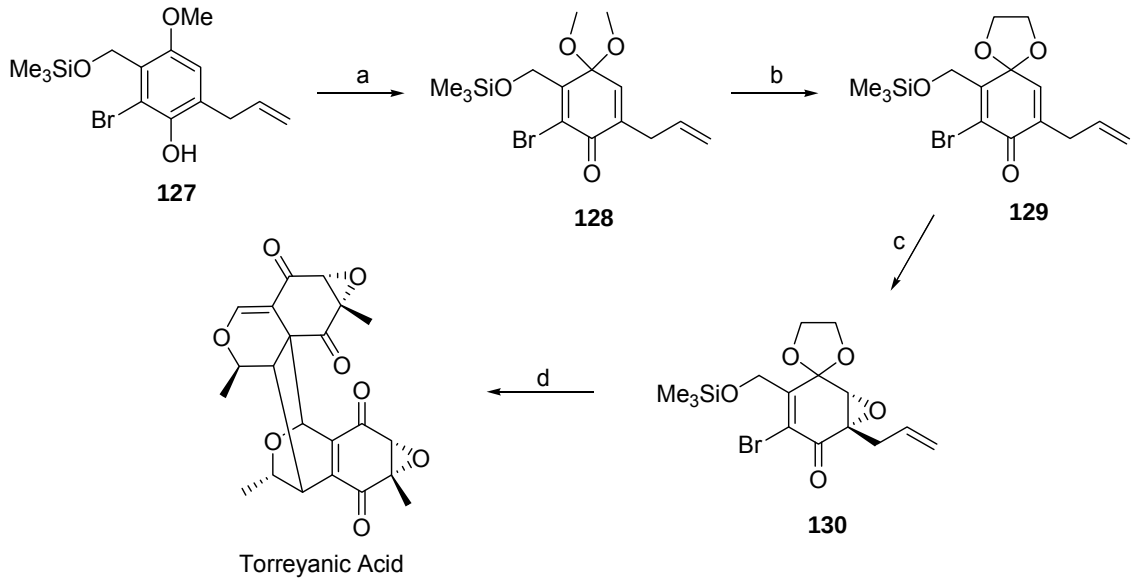


Figure 37. Natural products synthesized from masked p-benzoquinone ketals.

Porco[97] made use of a masked *p*-benzoquinone ketal to complete the total synthesis of torreyanic acid **124** (Figure 38). The construction of torreyanic acid begins with the oxidation of **127** with PIDA in the presence of MeOH, which results in the masked *p*-benzoquinone ketal **128**. This adduct is then transketalized to give the

more stable masked *p*-benzoquinone ketal **129**. Epoxidation was accomplished with freshly prepared anhydrous Ph_3COOH deprotonated with KHMDS. As a result, these conditions afforded the epoxide **129**. Subsequent Stille coupling with the vinyl bromide and deprotection under acidic conditions results in an immediate [4+2] dimerization, which upon oxidation with DMP furnished **124**.



a) PIDA, MeOH. b) $HO(CH_2)_2OH$, PPTS. c) Ph_3COOH, KHMDS. d) Stille, HF/MeCN, DMP.

Figure 38. Total synthesis of torreyanic acid.

Although the masked *p*-benzoquinone ketal is the most prominently studied substrate of cyclohexadienones, the knowledge base of its counterpart class *p*-quinols is much less developed.

1.7 p-Quinols and Their Natural Product Applications

Natural products from the structural types of griseofulvinoids, futoquinoids, sorbicillinoids and ananorosinoids are total natural product syntheses that were constructed using the *p*-quinol class of cyclohexadienones.[2] The total synthesis of griseofulvin from the family of griseofulvinoids was first accomplished in 1959.[100] Unfortunately, all methods of synthesizing griseofulvin resulted in a racemic

product. Later, Danishefsky[101] and Taub[102] found that compound **131** can undergo an oxidation reaction to form enone **132** which possessed a newly formed five membered lactone ring. Next, it was found that hydrogen added from the less hindered face of the enone **132** to afford **133** via a diastereoselective hydrogenation (Figure 39). Although griseofulvin had been constructed by a diastereoselective dearomatization of **131**,[102-105] a method to obtain an enantioselective dearomatization has yet to be developed.

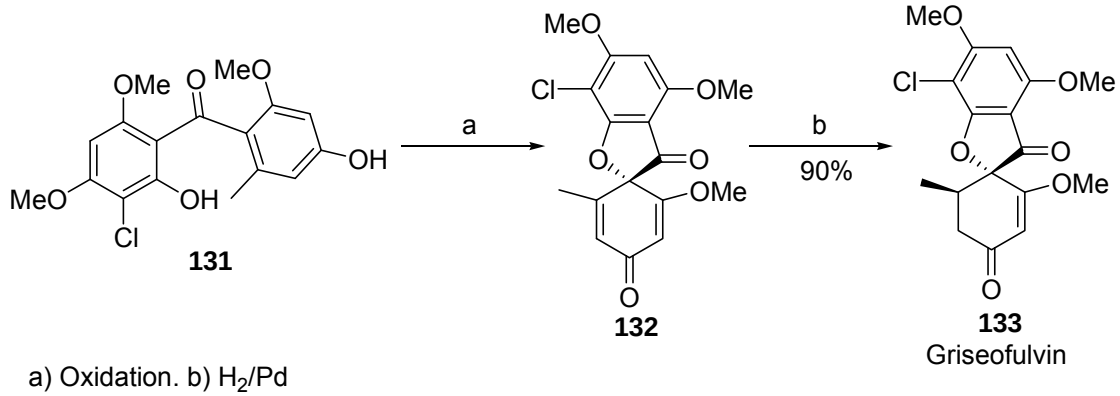
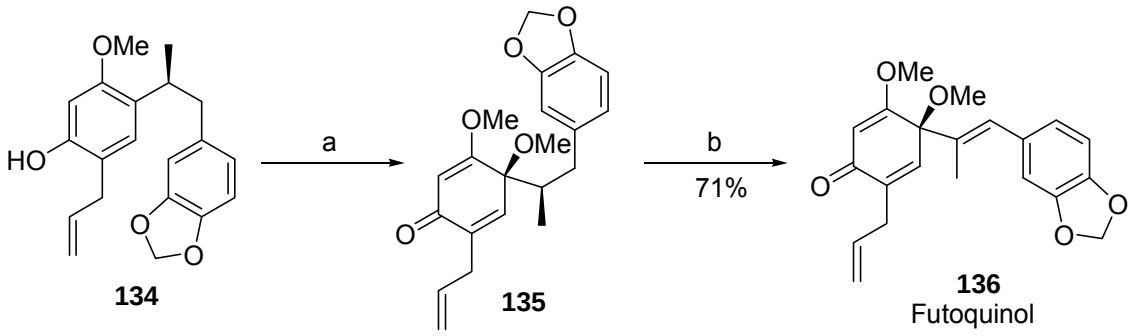


Figure 39. Synthesis of Griseofulvin.

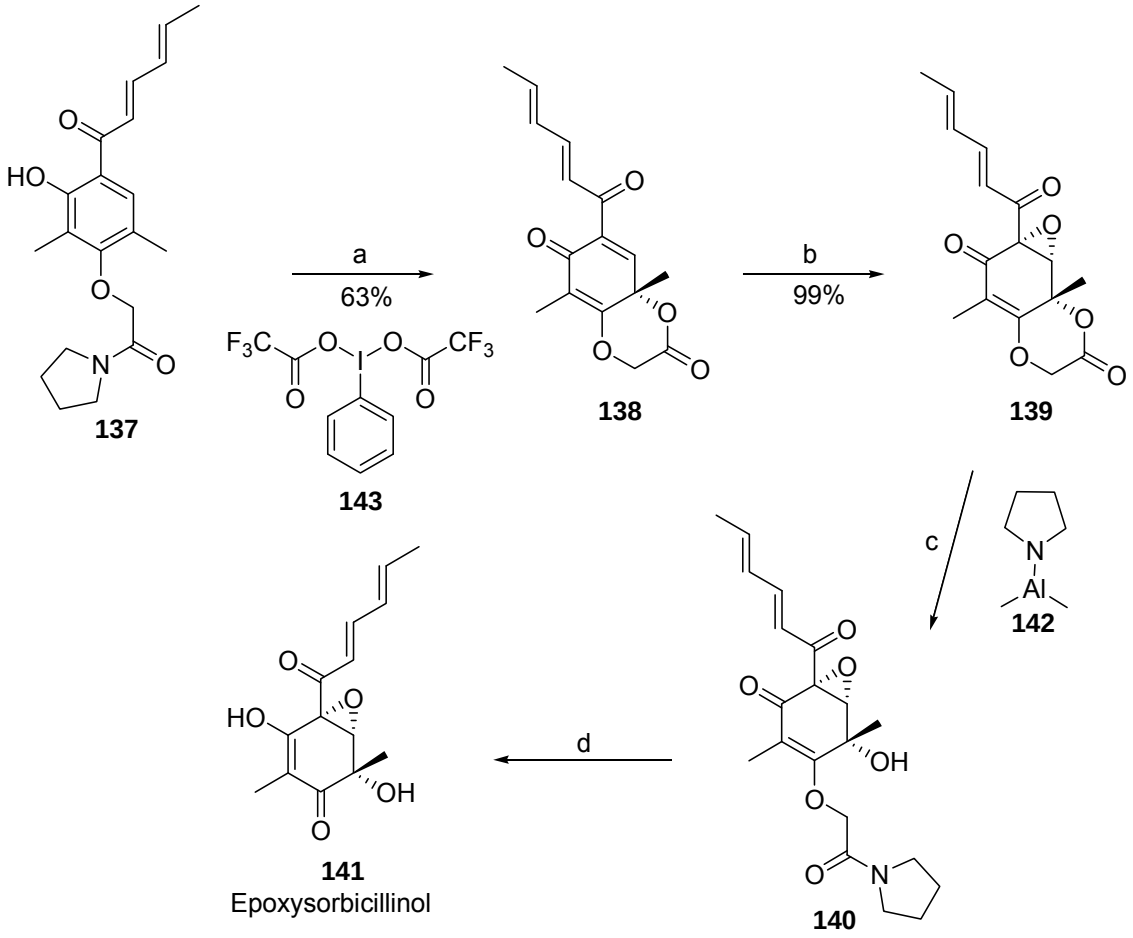
Yamamura synthesized several members of the futoquinoids class of natural products by an electrochemical oxidation in methanol.[106] As shown in Figure 40, the chiral phenol **134** was electrochemically oxidized to form one diastereomer of isodihydrofutoquinol **135**. Next, Yamamura discovered that exposing **135** to dehydrogenation with DDQ generated diastereomerically pure futoquinol **136**. Although futoquinol **136** had been synthesized by a diastereoselective electrochemical route of **134**, a method to obtain product **136** from an achiral starting material has yet to be invented.



a) Pt Anode, MeOH. b) DDQ.

Figure 40. Synthesis of Futoquinol.

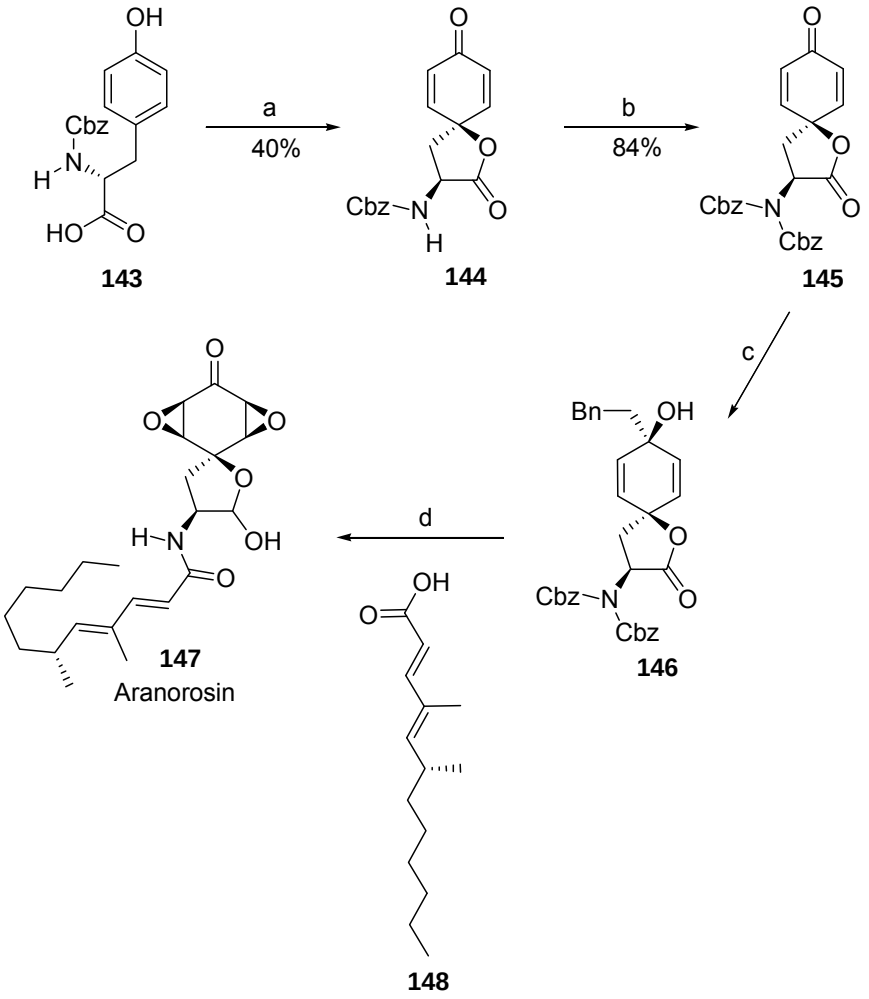
A member of the sorbicillinoid family, epoxysorbicillinol **141**, was synthesized by Pettus.[107] The synthesis began with the oxidation of the phenol **137** to provide **138**. Subsequently, the epoxide **139** as a single diastereomer was afforded by the treatment with of **138** with PhIO. The newly formed lactone product **139** was then treated with an alkyl aluminum reagent **142** to obtain an amide product **140**. Lastly, the natural product epoxysorbicillinol **141** was obtained by the reaction of the vinylogous ester **140** with $SnCl_4$ (Figure 41).



a) Phenyliodine(III) bis(trifluoracetate) (**143**) b) PhIO. c) Aluminum Species (**142**). d) $SnCl_4$.

Figure 41. Synthesis of Epoxysorbicillinol.

Aranorosin **147** from the family of ananorosinoids has been synthesized from *p*-quinol derivatives by Wipf,[108] McKillop,[109] and Hoshino.[110] Wipf reported *p*-quinol **144** could be synthesized via an oxidation of phenol **143** with the use of PIDA. Furthermore, Wipf reported that after protection of the nitrogen atom with a second Cbz residue to afford **145**, a 1,2-addition of benzyloxymethyl lithium to the carbonyl functionality produced the major diastereomer **146** in a 5:1 mixture of diastereomers. Next, directed epoxidations followed by the deprotection of protection groups and the addition of the remaining side-chain **148** to **146** provided the natural product aranorosin **147** (Figure 42).



a) PIDA. b) Cbz_2O. c) $BnCH_2Li$. d) 1. m-CPBA, 2. (**148**), Ph_2POCl, NMM, THF, 3. $NaBH_4$, $CeCl_3$.

Figure 42. Synthesis of Aranorosin.

p-Quinols and their derivatives have been used in some natural product total syntheses. Aranorosin, to the best of my knowledge, is the only natural product possessing a *p*-quinol motif that has been synthesized in an enantioselective manner. This synthesis was accomplished starting from chiral reagents. As a result, there is a necessity to develop other methods to attend to non-racemic *p*-quinol derivatives. In addition, if such methods were developed and available, several natural products could be synthesized in an enantioselective manner (Figure 43).

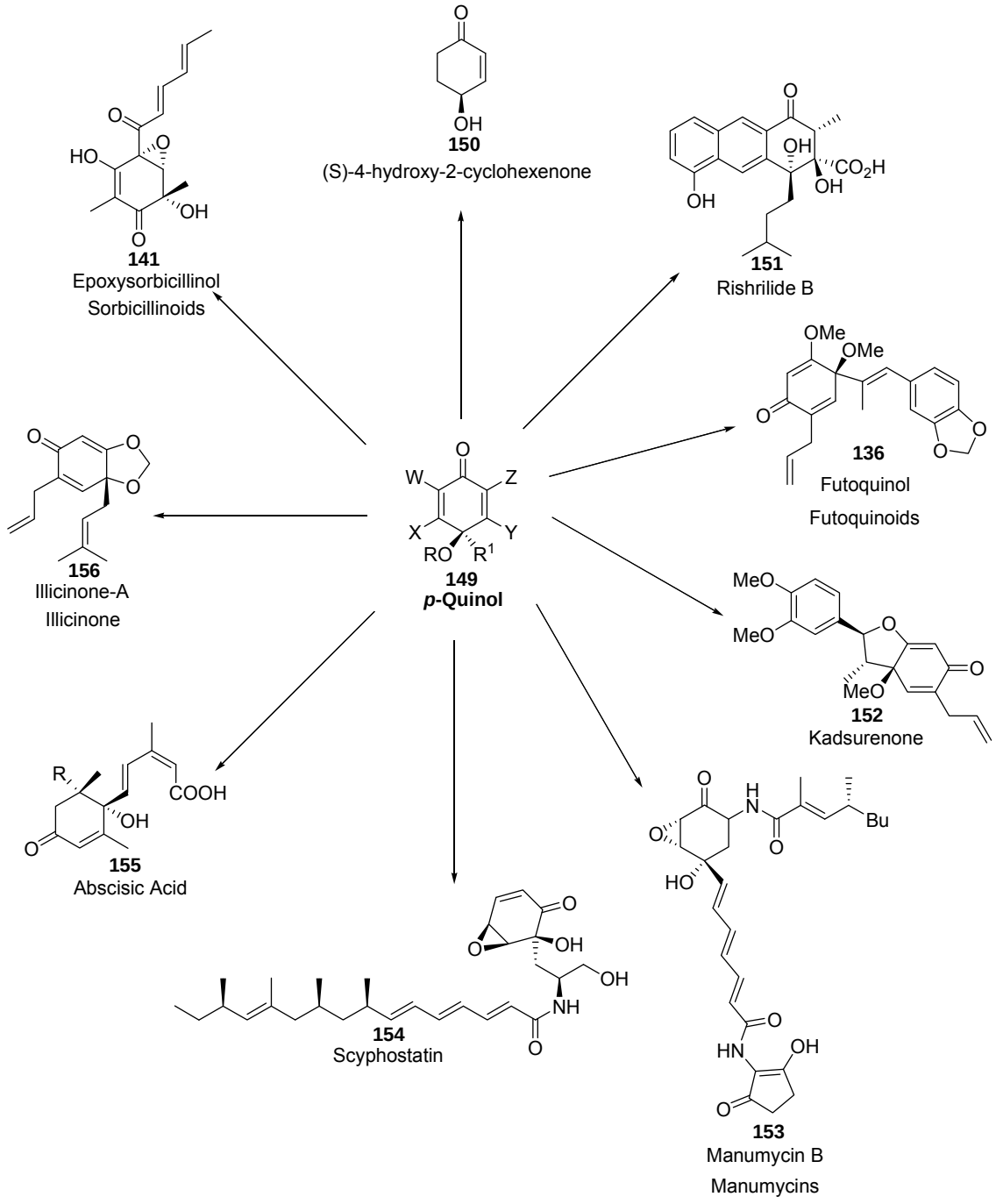
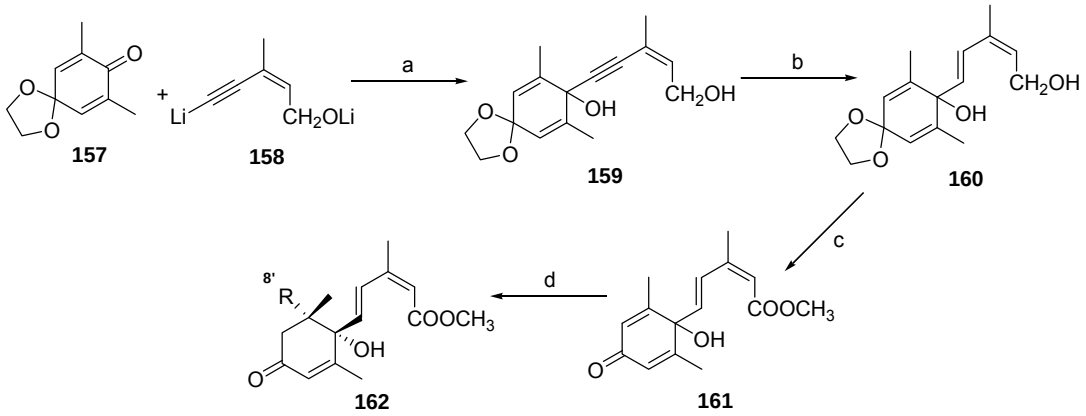


Figure 43. Enantioselective syntheses candidates from p-quinol intermediates.

Abscisic acid (ABA) is a plant hormone that regulates a wide range of pathways involved in plant growth, including the development and germination of seeds, transpiration, growth inhibition and adaptive responses to environmental

stress.[111] Metabolism of abscisic acid (ABA) in plants occurs principally through oxidation of one methyl of the gem dimethyl group of the cyclohexenone ring, that is syn to the hydroxyl group. ABA analogues that are altered at the 8'-carbon (a numbering system adopted in the plant hormone field), have been shown to act as plant growth regulators. The application of ABA itself as a plant growth regulator has been limited by its rapid catabolism in plants.[112] Abrams[112] reported the synthesis of various biologically active 8'-altered analogues where groups including a methoxymethyl, an ethyl, a methylene and an acetylene functionality have replaced the 8' gem methyl group. In particular 8'-acetylene ABA has shown exceptionally high biological activity and a prolonged lifetime over ABA. Abrams reported an improved synthesis of several 8'-substituted analogues using the synthesis in Figure 44.



a) 1,2-Addition. b) Reduction, Red-Al. c) MnO_2, NaCN, MeOH. d) RMgX.

Figure 44. Synthesis of MeABA analogues.[112]

The synthesis of MeABA proceeds in high yields and the final step is a diastereoselective addition reaction. The Grignard addition reaction occurs only at the 8'-position and is facially selective, through the direction by the hydroxyl moiety. The addition reaction is limited to reactive Grignard reagents, as increased temperatures result in the formation of an epoxide side product **164** (Figure 45).[112] Very reactive Grignard reagents such as allylmagnesium bromide produce a 1,2 addition product. In addition, Abrams[113] has found that the addition of a Lewis acid promotes the formation of the desired product **162**. However, the addition of a

Lewis acid has also been found to promote the formation of a rearrangement product **163**, the result of a double 1,2 migration of the alkenyl group in compound **161** (Figure 45).

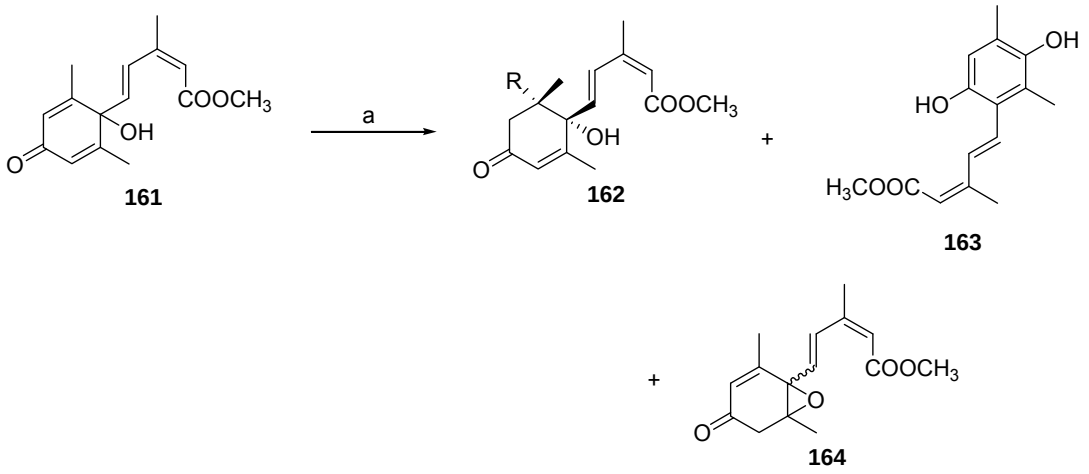


Figure 45. Grignard addition reaction and side products.

The Abrams improved ABA synthetic route produces a racemic product **162** from the final Grignard conjugate addition reaction to **161**. Therefore, an enantioselective synthesis of ABA via an enantioselective conjugate addition reaction would offer considerable commercial value as well as a more elegant synthesis and access the non-racemic product.

1.8 Proposal and Methodology

An overview introducing many different methods of performing an ECA to acyclic and cyclic dienones has been presented in this chapter. There is a necessity to establish a method to perform ECAs to cyclohexadienones, as the syntheses of numerous natural products could be developed using this type of addition reaction.[20] For example, the synthesis of ABA would greatly benefit from an ECA to p-quinols. One such system that has not been thoroughly investigated is ECAs to α,β-unsaturated β-disubstituted γ-trisubstituted ketones such as **165** (Figure 46).

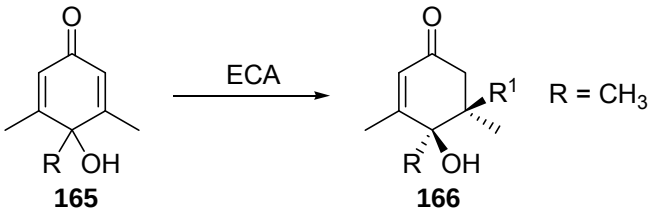


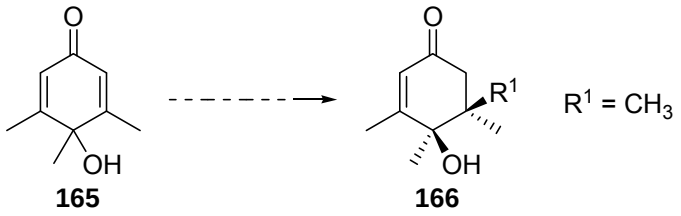
Figure 46. Proposed investigation study.

This investigation would provide some methodology studies about the construction of all-carbon quaternary stereocenters with the use of an α,β-unsaturated β-disubstituted γ-trisubstituted ketone substrate possessing a hydroxyl motif at the γ position. In addition, this study would benefit the total syntheses of some natural products, such as the total synthesis of ABA. There are many successful methods of performing an ECA to α,β-unsaturated ketones, however, there are very few methods of performing an ECA to cyclic α,β-unsaturated β -disubstituted ketones similar to **165** where R is an alkyl group or an alkenyl group as in the ABA intermediate **165**. Furthermore, very little is known about ECAs to substrates with a γ hydroxyl motif. Variables such as temperature, solvent, types of nucleophiles, and types of ligands will be very important in this study, as conditions that give high selectivity for one substrate may not work for an apparently similar substrate. Therefore, each new type of ECA reaction may require a methodology study to determine the feasibility of using that template for a planned targeted synthesis of **166**.

CHAPTER 2: RESULTS AND DISCUSSION

Reactions that produce enantio-enriched cyclohexadienone-derived natural products have been, and continue to be, of interest to many chemists.[2] The absence of general enantioselective methods using cyclohexadienone structures[109] has prevented their widespread use in total synthesis. Several reactions, documented in the literature, to create different types of possible tertiary stereocenters with excellent levels of enantiocontrol and chemical yields are known (see Introduction).

Enantioselective C-C bond formation reactions to produce all-carbon quaternary stereocenters are much less well known.[1] Reactions developed by Tomioka,[22] Feringa,[39,75] Hoveyda,[84] Alexakis,[18] Chong,[77] Hayashi[91] and Ellman[82] were surveyed in order to perform an ECA to cyclohexadienone **165**. Described herein were my efforts to: i) perform an ECA to **165** by means of external chiral ligand methods and ii) perform an ECA to **165** via a sulfinyl imine chiral auxiliary.



165 **166**

Figure 47. Proposed ECA to compound **165**.

The symmetrical nature of compound **165** presents a difficult challenge. In order to perform an ECA to the achiral compound **165** the direction of attack must distinguish between the Re and Si faces of the molecule as well as the molecule's pro-R and pro-S reaction sites. The reaction between compound **165** and a nucleophile other then a methyl group will result in the creation of two stereocenters. Thus, the reaction between compound **165** and a nucleophile **R,** where $R \neq CH_3$, can result in four potential stereoisomers (Figure 48).

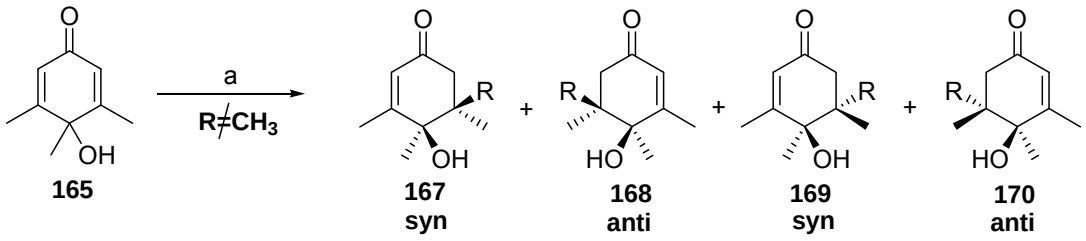


Figure 48. The four possible products from a conjugate addition reaction to **165**.

However, if the nucleophile is a methyl group only one stereocenter is formed and only two potential stereoisomers can be formed (Figure 49). In some cases, a reaction to compound **165** may be diastereoselective and favour only one face of the molecule. For example, in a Grignard reaction with compound **165** the hydroxyl moiety may assist the reaction to produce facial selectivity and in turn the products **171** and **172**.

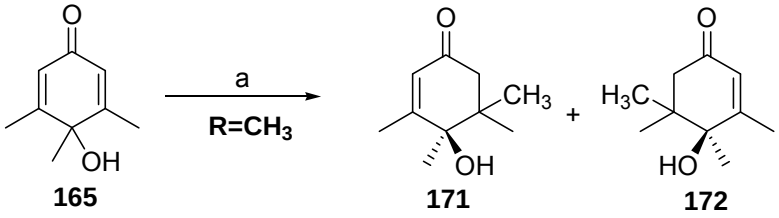


Figure 49. The two possible products from a conjugate addition reaction to **165** where R=CH_3.

2.1 Determination of Enantiomeric Ratios.

The purpose of this study was to develop an enantioselective conjugate addition reaction. As a result, an analytical method to measure the proportion of different enantiomers was required. The key principle in measuring the ratio of enantiomers in a sample is to situate them in a chiral environment and exploit some difference in the new diastereoisomeric species.[114] All techniques for determining selectivity are either chromatogragraphic or involve coupling enantiomers.

Chromatographic techniques include HPLC and GC using chiral columns. Coupling methods involve covalent or non-covalent bonding with an enantiomerically pure compound.[114] To separate enantiomers of **166** a number of HPLC chiral columns were tried, with nonpolar, polar organic and reversed phase solvents systems. One column Pirckle (R,R)-Whelk-01 gave a reasonable resolution. The Whelk-01 column was reported to be useful for the separations of underivatized enantiomers in a number of families including amides, epoxides, esters, ureas, carbamates, ethers, aziridines, phosphonates, aldehydes, ketones, carboxylic acids, alcohols, and non-steroidal anti-inflammatory drugs.[115] Abrams112 reported the use of HPLC with the chiral Whelk-01 column to separate the enantiomers of the ABA analogue **162**, a similar system to **166**. Using the same literature experimental conditions as a starting point, enantiomers of **166** were separated by HPLC using normal phase solvents hexane and isopropanol in combination with a Pirckle (R,R)-Whelk-01 chiral column and an isocratic solvent mixture. The analytes were detected by UV light at wavelength 230 nm which was the maximum absorption of the α,β-unsaturated ketone chromophore. The resulting peaks of the chromatogram were then integrated. Chromatograms from a racemic sample of **171** and **172** displayed a peak area ratio of 1:1 (Figure 50). Non-racemic samples (Figure 51) were analyzed with the same method and the enantiomeric excess (ee) was calculated using the following relationship.

$$ee = (| (R - S) | / (R + S)) \times 100\% \quad (A.1)$$

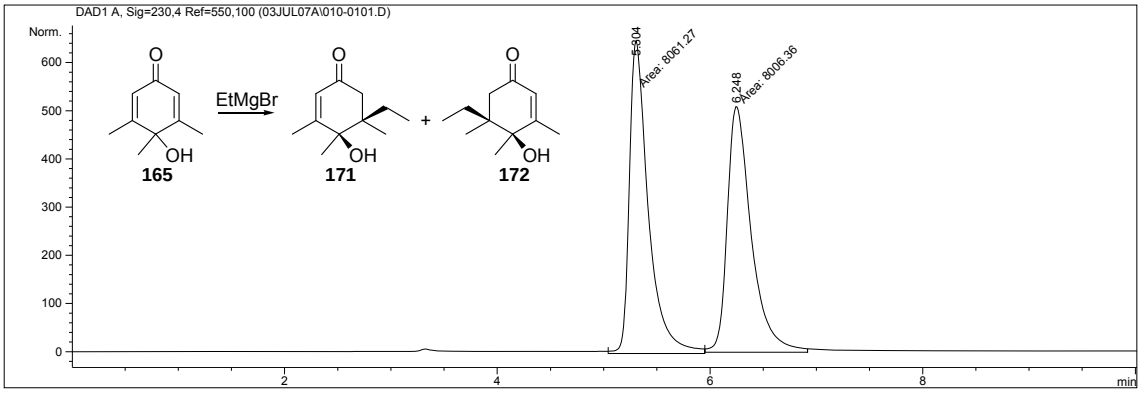


Figure 50. HPLC chromatogram of a racemic sample of **171** and **172** produced from a facially selective Grignard addition reaction with **165** and ethylmagnesium bromide.

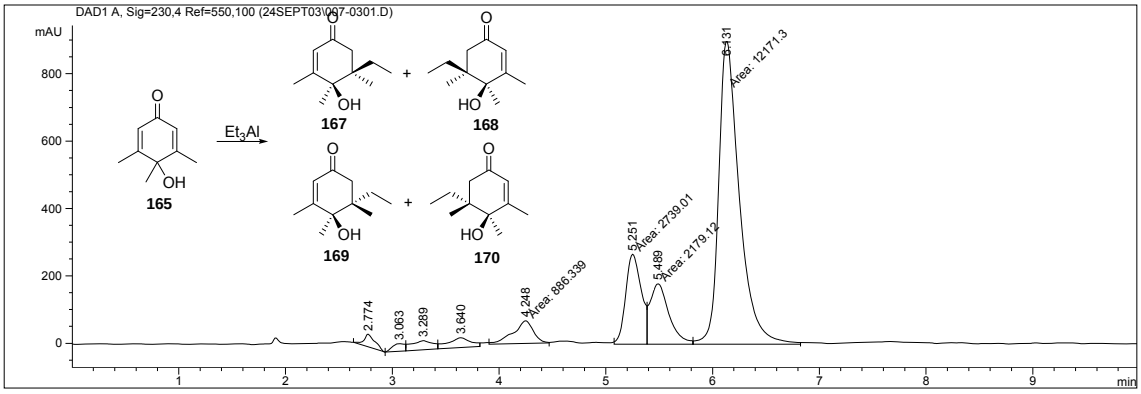
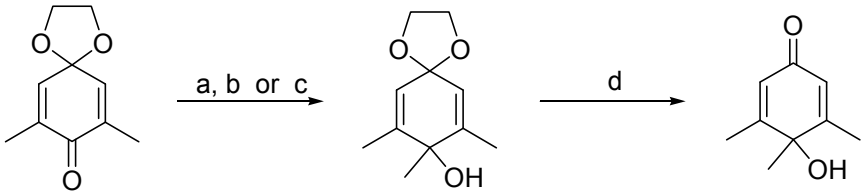


Figure 51. HPLC chromatogram showing of a non-racemic sample of **167**, **168**, **169** and **170** produced from a triethylaluminum reaction with **165** with a phosphoramidite ligand (Table 15, Entry 2).

2.2 Enantioselective Conjugate Addition (ECA) Methods Using an External Chiral Ligand

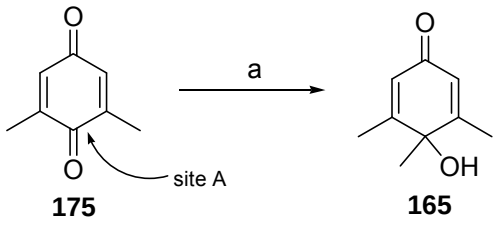
Multi-gram quantities of 4-hydroxy-3,4,5-trimethylcyclohexa-2,5-dienone **165** were required for this project. To date, two methods of synthesizing compound **165** have been reported. Liotta[116] reported the first synthesis of compound **165** via a 1,2 addition reaction using MeLi and 2,6-dimethylbenzoquinone. Imamoto also reported the synthesis of compound **165** by a 1,2 addition reaction to compound **173** using MeLi and $CeCl_3$. Compound **173**, 2,6-dimethylbenzoquinone monoketal, was commercially available. This compound was reported to be prepared by an oxidation reaction between 2,6-dimethylphenol, ethylene glycol and iodobenzene diacetate[117]. Thus, using compound **173** as a starting point, the two precedent reactions were employed to produce 4-hydroxy-3,4,5-trimethylcyclohexa-2,5-dienones were synthesized **165** (Figure 52).



a) MeLi·LiBr, THF, -78°C. b) MeLi·LiBr, TMEDA, THF, -107°C. c) MeLi, $CeCl_3$, THF, -78°C. d) 10% HCl, THF, RT.

Figure 52. Conditions to synthesize dienone **165**.

The general procedure for the synthesis of **174** was performed by a 1,2 addition reaction of MeLi·LiBr at low temperature (-78°C) to **173**. The crude product compound **174** was purified by crystallization and followed by the removal of the ketal functionality with dilute hydrochloric acid to give cleanly **165** in an overall yield of 88%. Liotta[116] observed that the reaction between 2,6-dimethylbenzoquinone and MeLi in the presence of tetramethylethylenediamine (TMEDA) proceeded in a 1,2 addition fashion at the more hindered position. Liotta explains this phenomenon by the fact that small nucleophiles such as a CH_3^-, and only weakly solvated, electronic factors dominate the transition state, resulting in a regioselective addition to the more electrophilic carbonyl carbon (site a) (Figure 53). However, Liotta also noted that in the case of 2,6-dimethylbenzoquinone **175**, the 1,2 addition reaction of a methyl carbanion in the absence of TMEDA occurs at the less hindered carbonyl site. In this case the less hindered site was protected as ketal **173** and 1,2 addition reactions performed on **173** to produce **174** in the presence and absence of TMEDA resulted in 85% and 88% yields, respectively. The protection of the less hindered carbonyl of 2,6-dimethylbenzoquinone with a ketal permits only one location for a desired 1,2 addition reaction to take place. Therefore, large scale 1,2 addition reactions to **174** omitted the use of TMEDA as the yields of the two reactions were comparable.



a) MeLi·LiBr, TMEDA, THF, -107°C.

Figure 53. Liotta's regioselective 1,2 addition to compound **175**.

Imamoto[118] reported that 1,2 addition reactions of organolithium reagents to α,β-unsaturated carbonyl compounds such as **175** can be effected with high regioselectivity with the use of anhydrous $CeCl_3$. Imamoto's 1,2 addition of MeLi to compound **173** produced a 97% yield. This result was validated as we achieved a similar yield of 92%. Later, Imamoto suggested that this result supported Liotta's[119] hypothesis that stated the reaction takes place via a single electron transfer mechanism based on the relationship between the rate of the reaction and the size of the donating carbanion group. Imamoto's $CeCl_3$ addition reaction led to a slightly higher yield then Liotta's MeLi method. However, due to difficulties in handling anhydrous $CeCl_3$ and the fact that the $CeCl_3$ reaction did not result in a significantly higher yield then the MeLi reaction, Imamoto's reaction method was abandoned.

The product collected after the addition reaction and the removal of the ketal functionality was structurally elucidated by ^{1}H NMR, ^{13}C NMR, IR, MS and UV. The product was shown to be compound **165**. Compound **165** was described in the literature as a known compound however, no characterization data was reported. The ^{1}H NMR spectrum demonstrated 3 expected peaks at 5.96 ppm, 2.08 ppm and 1.42 ppm (Figure 54). These peaks represented the olefinic (HC-6, HC-2), (Table 1, Entry1), vinyl methyl (H_3C-7, H_3C-9), (Table 1, Entry 2), and remaining methyl (H_3C-8) protons (Table 1, Entry 3), respectively. The ^{13}C NMR spectrum further supported the structure by displaying the correct number of magnetically nonequivalent carbons. For example, **165** showed 4 carbon peaks representing the diene ring at 186.05 ppm (C-1'), 164.38 ppm (C-3', C-5'), 125.31 ppm (C-2', C-6'), and 71.38 ppm (C-4'). In addition, the ^{13}C NMR spectrum demonstrated the remaining three methyl group carbon atoms by 2 peaks at 25.89 ppm (C-8') and

18.19 ppm (C-7', C-9'). The IR spectrum revealed the presence of a hydroxyl stretch at 3408 cm^{-1}, an α,β-unsaturated carbonyl stretch at 1669 cm^{-1} and an alkene stretch at 1618 cm^{-1}. The strong alkene stretch found in the IR spectrum is commonly observed in conjugated cyclohexadienones.[117] Further proof was attained from the electron impact mass spectrum where the molecular ion peak was found to be 152.0839 (calc. 152.0837). Lastly, the UV spectrum of **165** portrayed a single absorption at 237 nm with an extinction coefficient of 1.3 x 10^4 $M^{-1}{\cdot}cm^{-1}$. These two values are comparable to the known literature values of 228 nm and 1.2 x 10^4 $M^{-1}{\cdot}cm^{-1}$ for the similar *p*-dienone structure 4-hydroxy-4-methylcyclohexadien-1-one.[120]

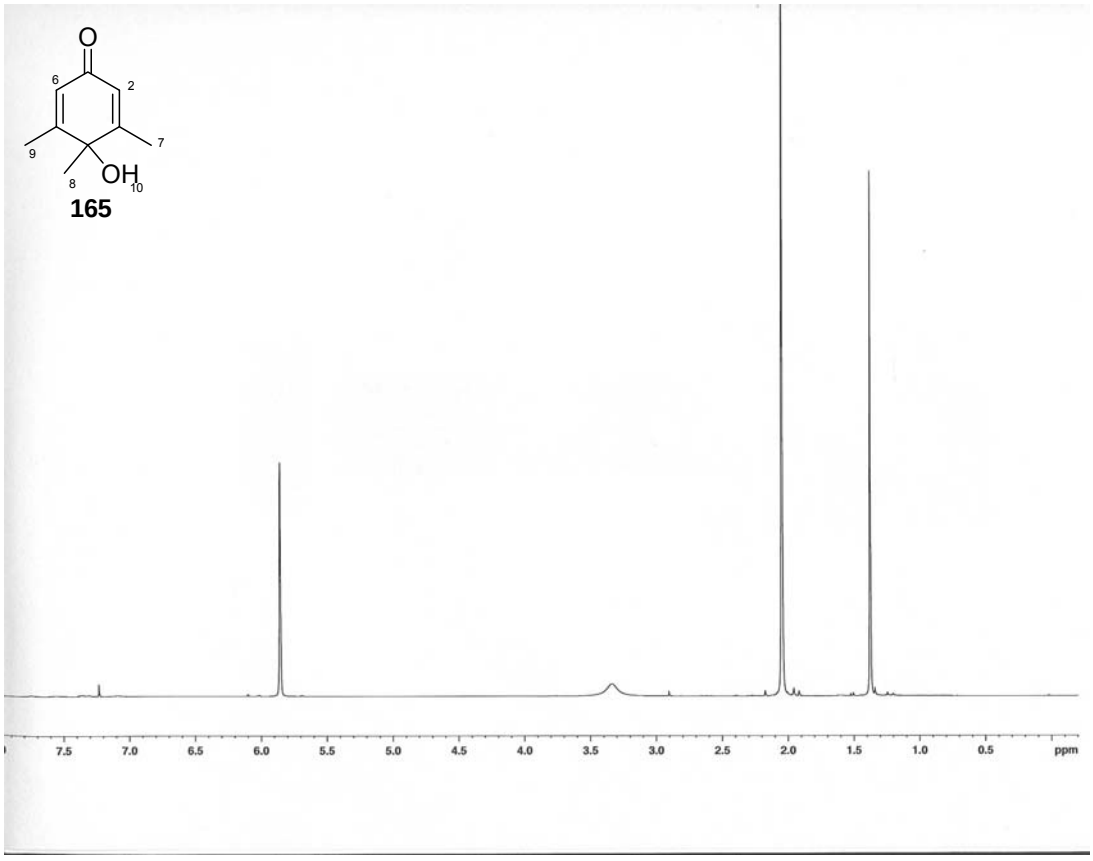


Figure 54. ^{1}H NMR spectrum of compound **165**.

Table 1. Chemical shifts of the ^{1}H NMR spectrum of compound **165**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-2, HC-6	5.96	2H, s
2	H_3C-7, H_3C-9	2.08	6H, s
3	H_3C-8	1.42	3H, s

2.1.1 Alkyllithium Conjugate Additions.

The objective of this study was to develop a stereoselective addition to the 4-hydroxy-3,4,5-trimethylcyclohexa-2,5-dienone **165** system via an ECA (Figure 46). A decision was made to begin this project by attempting reactions on readily available simpler model systems such as α,β-unsaturated acyclic enones **27** and a more common simple cyclic enone, 2-cyclohexen-1-one **3**. These reactions included organolithium, Grignard, organozinc, organoaluminum and boronic acid addition reactions. The addition reactions were firstly validated to confirm the relevant literature report and to ensure that the reagents and techniques were adequate. If the addition reaction was successfully repeated, the reaction was then employed with substrate **165**.

ECA reactions to enones with organolithium reagents and a chiral diamine ligand are precedented[22]. Organolithium reagents are also known to possess high reactivity and favour a 1,2 addition reaction with cyclic enone structures.[121] The reactivity of organolithium reagents is affected by complexation with different solvents and additives. Such effects have usually been attributed to changes in the aggregation states and solvation of the lithium species involved.[121] It is well established that many organolithium reagents form various aggregates in ethereal solutions, and that stronger coordinating solvents tend to move the average aggregation state to lower numbers. Lithium demonstrates a strong propensity for tetracoordination.[122] As a result, MeLi is a monomeric lithium compound that can coordinate three solvent molecules. The biggest structural change for solvent

coordinated MeLi occurs when the carbon-lithium bond is broken and the contact ion pair (CIP) monomer is converted to a separated ion pair (SIP). A CIP is a pair of oppositely charged ions held together by a Coulomb attraction without formation of a covalent bond, whereas an SIP is a pair of oppositely charged ions not held together. This conversion of a CIP to an SIP causes a dramatic reactivity effect.

The effect of additives in favoring 1,4- over 1,2-addition of some types of lithium reagents under conditions of kinetic control was first reported in 1977.[123] The proposal was made that this effect of additives was a consequence of conversion from CIP to SIP structures.[123-126] Several computational studies that examined the addition of monomeric organolithium species to carbonyl compounds have predicted cyclic 4-membered transition states.[127-129] Such cyclic transition states cannot operate for 1,4-additions to cyclic enones.[121] However, once ion separation by solvent or additive coordination is accomplished, 1,4-addition can occur smoothly to form the more stable 1,4-adduct (Figure 55). This hypothesis was further supported by evidence produced by experiments performed at low temperatures where a 1,4-addition reaction was favoured.[123] Generally SIP states are favoured over CIP states at low temperatures.

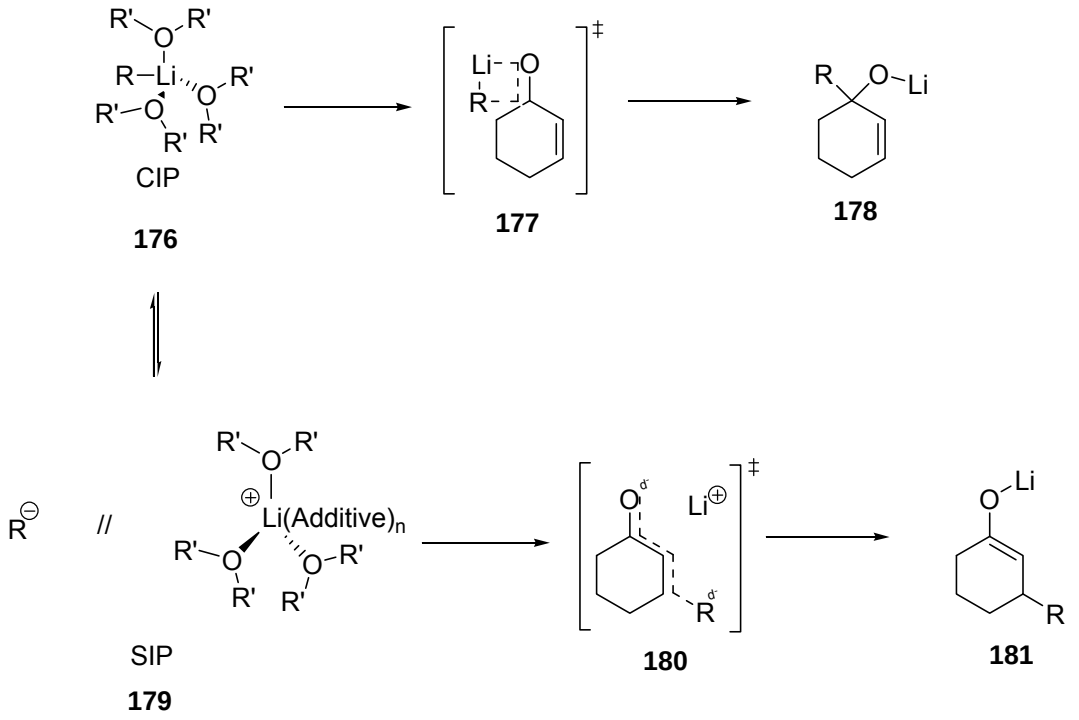
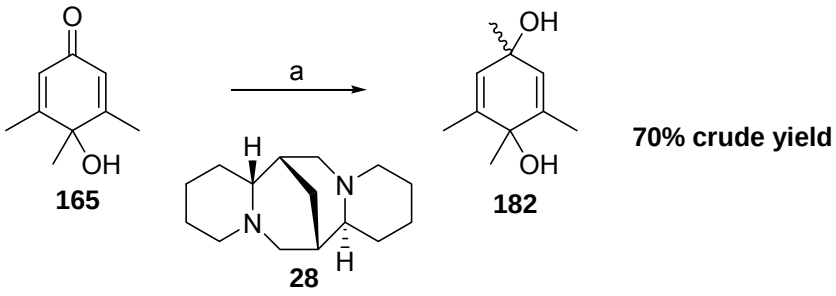


Figure 55. Mechanistic hypothesis for the regioselectivity of organolithium additions to enones.[123]

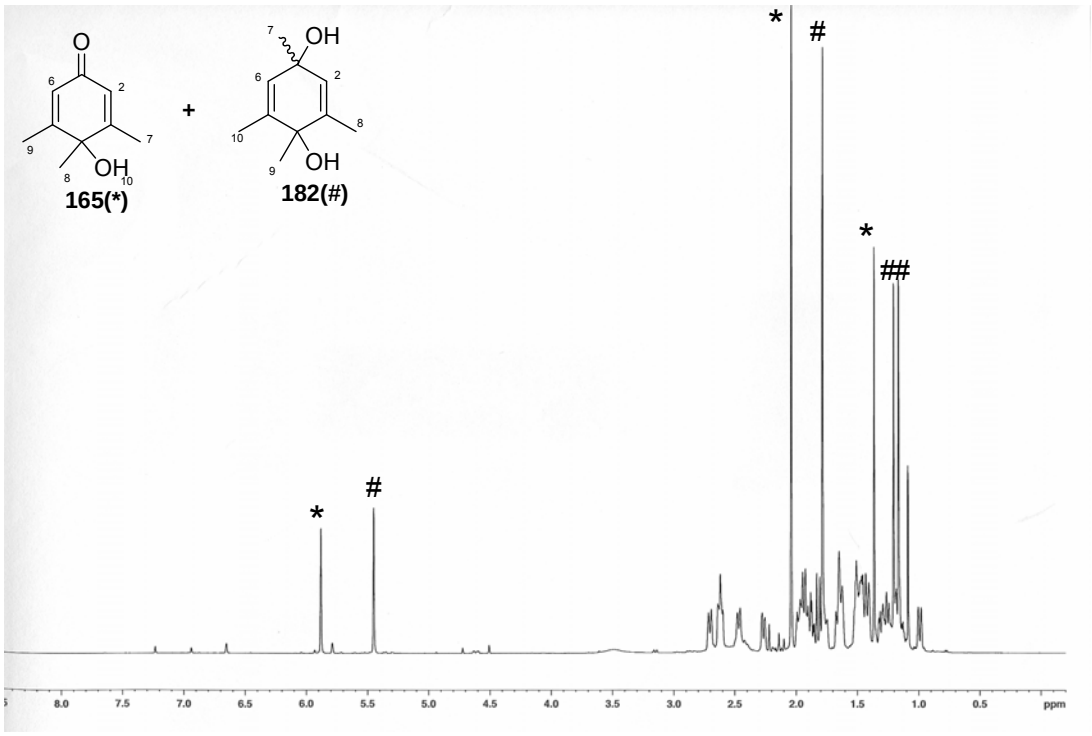
The substrate **27** (Figure 7) published by Tomioka was foreseen as a reasonable precedent for an ECA reaction. Although compound **27** was acyclic it was thought to be a good starting point and perhaps a structure that would have similar reactivity to that of a cyclic substrate. The sterically crowded type structure, with the presence of a trisubstituted phenyl group, of compound **27** was thought to be similar to the rigid structure of compound **165**. In addition, the catalyst **28** was readily available. Thus, the conditions published by Tomioka were then applied to **165**. Unfortunately, the crude product only displayed a 1:1 diastereomeric mixture of two 1,2 addition products in 70 % yield (Figure 56).



a) MeLi, (-)-sparteine (**28**), PhMe, -78°C

Figure 56. ECA to **182** using organolithium reagents.

The ^{1}H NMR spectrum of the crude product and comparison to the known ^{1}H NMR spectrum of compound **182** confirmed the presence of a mixture of 1,2 addition products by the appearance of 4 expected peaks at 5.38 ppm, 1.85 ppm, 1.19 ppm and 1.15 ppm (Figure 57).[130] The peak at 5.38 ppm represented the olefinic protons (HC-2, HC-6) of the 1,2 addition products (Table 2, Entry1). The vinyl methyl protons (H_3C-8, H_3C-10) of the mixture of products were represented by a large singlet peak at 1.85 ppm (Table 2, Entry 2). The remaining methyl group protons (H_3C-7, H_3C-9) were represented by two singlet peaks at 1.19 and 1.15 ppm (Table 2, Entries 3 and 4). The crude ^{1}H NMR spectrum also displayed the presence of compound **165** (*) and (-)-sparteine **28**. Purification was then attempted in order to isolate the 1,2 addition product from any remaining starting material by chromatography and distillation techniques but, the crude product **182** decomposed.



(*)Denotes compound **165** and (#) denotes compound **182**.

Figure 57. ^{1}H NMR spectrum of the crude reaction product containing a diastereomeric 1,2 addition mixture **165**.

Table 2. Chemical shifts of the ^{1}H NMR spectrum of compound **182**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)	Literature Value[133] (ppm)
1	HC-2, HC-6	5.38	2H, s	5.35
2	H_3C-8, H_3C-10	2.08	6H, s	2.05
3[a]	H_3C-7, H_3C-9	1.19	3H, s	1.17
4[b]	H_3C-7, H_3C-9	1.15	3H, s	1.13

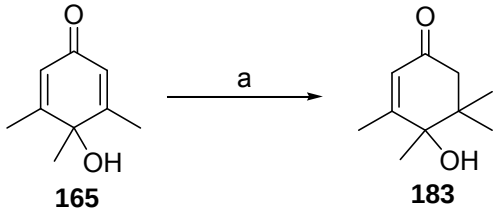
[a]H_3C-7, H_3C-9 protons of the first diastereomer. [b]H_3C-7, H_3C-9 protons of the second diastereomer.

Tomokia[22] observed that when excess alkyllithium reagent was added to the reaction with compound **27**, the 1,4 addition reaction would produce a racemic product. As a result, the lithium species would compete with a chelated lithium-ligand species to form an selective product. Tomokia added that preferential formation of the chelated complex with alkyllithium and a chiral ligand was necessary for the reaction to be highly efficient. As a result, Tomokia selected the

chiral diamine **28** ligand to satisfy the above requirement, because nitrogen atoms have a high coordinating ability to lithium. However, when the diamine ligand was utilized in combination with our cyclic system, the 1,4-addition reaction did not proceed. Thus, the organolithium reagent may have been acting as a CIP in a higher aggregation state. Therefore, a possible higher aggregation state in combination with a complex β,β-disubstituted cyclic system accounts for the 1,2-addition mechanism to **165** to produce **182**.

2.1.2 Grignard Conjugate Additions.

Conjugate addition reactions using Grignard reagents are precedented.[39,112] Reactions aimed at synthesizing racemic compound **183** were performed (Figure 58) and the results are summarized in Table 3.



a) MeMgBr, THF, -78°C.

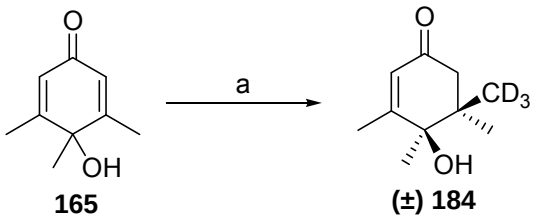
Figure 58. MeMgBr Grignard addition reaction to produce racemic **183**.

Table 3. Validating the reaction conditions using Grignard reagents reported by Feringa.

Entry	Catalyst	T (°C)	t (h)	Cu Salt	Grignard	Solvent	Yield (%)
1	--	-78	5	--	MeMgBr	THF	70
2	--	-78	5	--	CD_3MgI	THF	55

Compound **165** was alkylated in modest yields to obtain a racemic mixture, compound **183**. Compound **183** was previously reported but not characterized.[130] As a result, compound **183** was structurally characterized by ^1H NMR, ^{13}C NMR, IR, MS and UV. The ^1H NMR spectrum demonstrated 8 expected peaks at 5.79

ppm, 2.36 ppm, 2.31 ppm, 2.00 ppm, 1.55 ppm, 1.37 ppm, 1.06 ppm and 1.05 ppm (Figure 60). The singlet peak at 5.79 ppm (Table 4, Entry 1) and the two doublets at 2.36 ppm and 2.31 ppm (Table 4, Entries 2 and 3) represented the olefinic (HC-2, HC-6) protons respectively. The vinyl methyl (H_3C-7) (Table 4, Entry 4), and the three remaining methyl (H_3C-8, H_3C-9, H_3C-10) (Table 4, Entries 6, 7 and 8) protons were found to be represented by singlet peaks at 2.00 ppm, 1.37 ppm, 1.06ppm and 1.05 ppm, respectively. The ^{13}C NMR spectrum further supported the structure by revealing 10 peaks representing the correct number of magnetically nonequivalent carbons. For example, **183** showed 4 carbon peaks representing the 4 methyl groups at 23.84 ppm (C-8'), 22.88 ppm (C-9'), 22.58 ppm (C-10') and 19.18 ppm (C-7'). In addition, the ^{13}C NMR spectrum demonstrated the remaining 6 carbon atoms representing the ring structure by 6 peaks at 197.95 ppm (C-1'), 165.50 ppm (C-3'), 125.98 ppm (C-2'), 50.18 ppm (C-4'), 40.80 ppm (C-6') and 29.70 ppm (C-5'). The IR spectrum revealed the presence of a hydroxyl stretch at 3393 cm^{-1} and a carbonyl stretch at 1643 cm^{-1}. However, the alkene stretch found in the IR spectrum of compound **165** was absent in the IR spectrum of compound **183**. Further proof was attained from the electron impact mass spectrum, where the molecular ion peak was found to be 168.1150 (calc. 168.1150). Lastly, the UV spectrum of **183** produced a single absorption at 235 nm and an extinction coefficient of 1.4 x 10^4 $M^{-1}\cdot cm^{-1}$. These two values are comparable to the known literature values of a α,β-unsaturated ketone chromophores.[131]



165 **(±) 184**

a) CD_3MgBr, THF, -78°C.

Figure 59. Grignard addition using deuterium labeled MeMgBr reaction to **165**.

Using deuterium labeled MeMgBr, a Grignard addition reaction was performed to produce **184** (Table 3, Entry 2) (Figure 59). The Grignard experiment was conducted to confirm the facial selectivity of the reaction and to distinguish the

gem dimethyl signals in the ^{1}H and ^{13}C NMR spectra. The product **184** of the deuterium labeled Grignard experiment demonstrated an ^{1}H NMR spectrum similar to that of compound **183**. However, the ^{1}H NMR spectrum of **184** demonstrated the disappearance of a methyl group peak (Figure 61). This result also suggested that the methyl or deuteryl group was adding to **165** on the same face as the hydroxyl moiety.

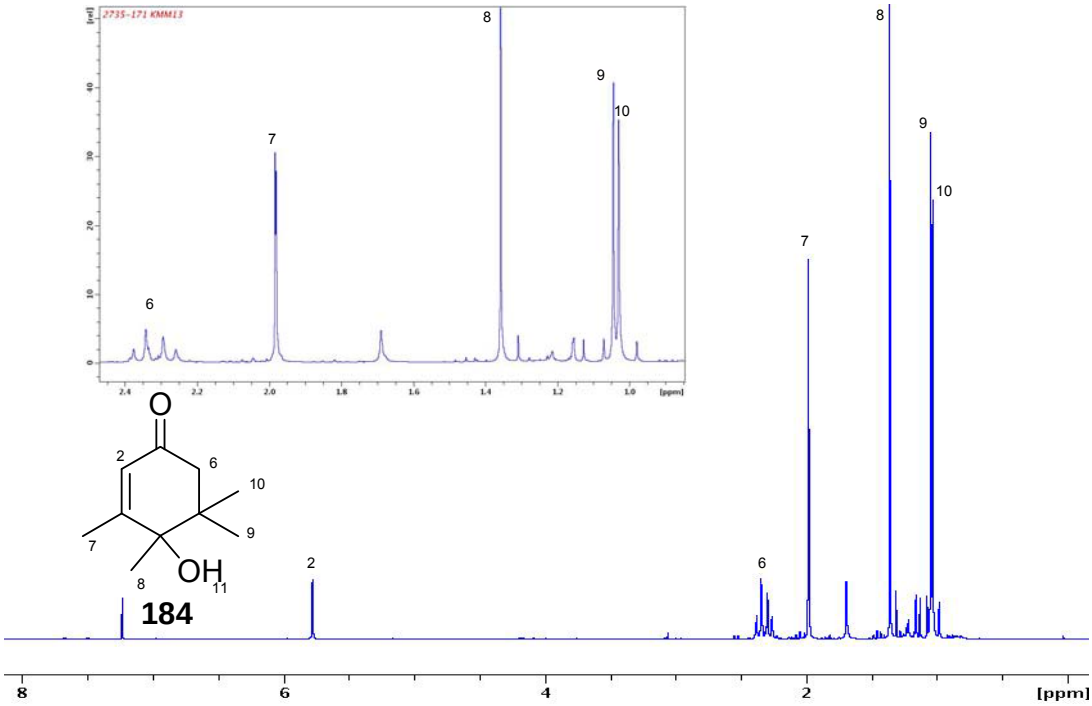


Figure 60. ^{1}H NMR spectrum of compound **183**.

Table 4. Chemical shifts of the ^{1}H NMR spectrum of compound **183**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-2	5.79	1H, s
2	HC-6	2.36	1H, d, J = 17.1
3	HC-6	2.31	1H, d, J = 17.1
4	H_3C-7	2.00	3H, s
5	HO-11	1.55	1H, s
6	H_3C-8	1.37	3H, s
7	H_3C-9	1.06	3H, s
8	H_3C-10	1.05	3H, s

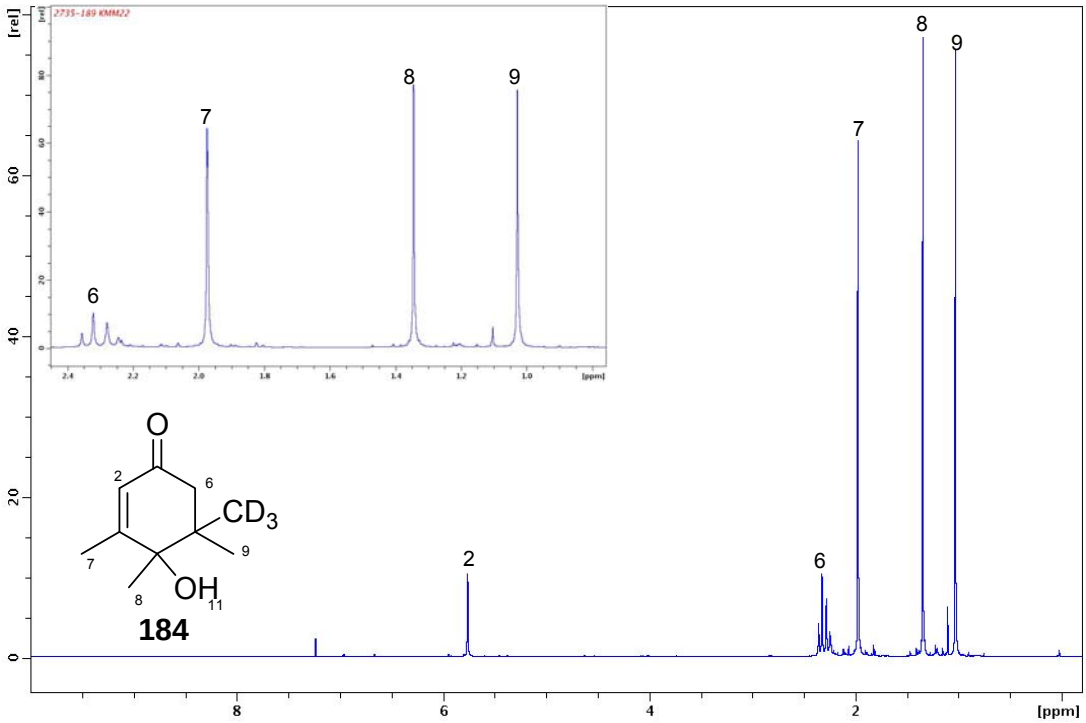


Figure 61. ^{1}H NMR spectrum of compound **184**.

Facial diastereoselectivity to *p*-quinol **165** type structures is precendented.[90,112] Carreno[90] reported that the reaction between cyclohexa-2,5-dienone **100** containing a chiral auxiliary and trimethylaluminum proceeds with complete facial diastereoselectivity (Figure 62). The methyl group was added to the same face containing the hydroxyl moiety.

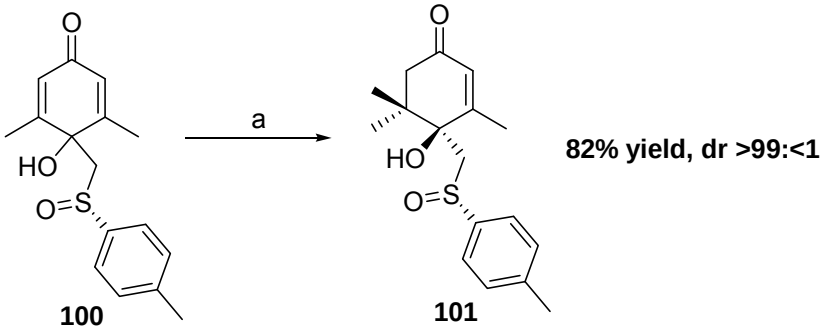
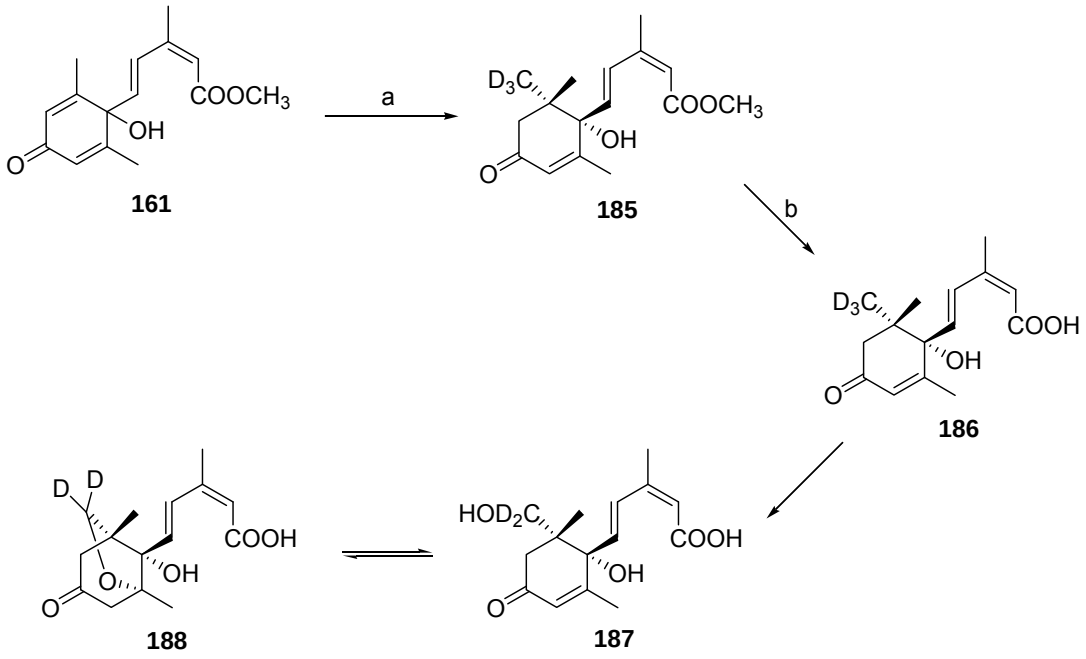


Figure 62. Carreno's 1,4-addition to **100**.

Abrams[112] reported a conjugate addition reaction to a *p*-quinol **161** type structure as the final step in their total synthesis of ABA and ABA analogues. Unlike Carreno, the Abrams group made use of Grignard reagents to perform this addition reaction. The conjugate addition reaction to **161** with a deuterium containing Grignard reagent was shown to react with facial diastereoselectivity (Figure 63). Abrams made use of feeding studies of corn suspension cells to confirm facial selectivity.[112] Corn cells have the enzyme ABA 8'-hydroxylase which is an enzyme that has high activity for the metabolism of ABA. Specifically the enzyme oxidizes ABA **186** to form 8'-OH ABA **187**. The 8'-OH ABA **187** then undergoes a spontaneous 1,4 addition to form phaseic acid **188**. The isolated phaseic acid from the corn cells was found to contain two deuterium atoms which confirmed that the deuterium labeled Grignard reagent had added to compound **161** diastereoselectively.

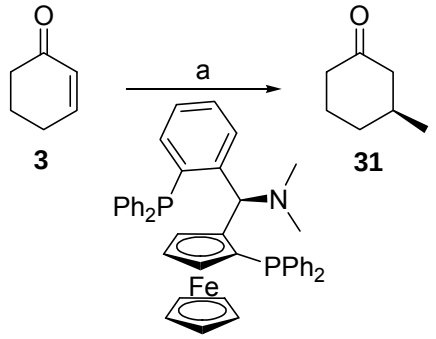


a) CD_3MgBr, THF, -78°C. b) KOH, EtOH, H_2O 50°C.

Figure 63. Abrams conjugate addition to **161**[115].

Enantioselective conjugate addition reactions using Grignard reagents are precedented.[39] A short study aimed at repeating the reported reaction conditions by Feringa was launched. The results are summarized in Table 5. The reaction

involved Grignard reagents, 2-cyclohexen-1-one **3** and a ferrocene-based ligand called Taniaphos **32** (Figure 64).



a) MeMgBr, Taniaphos (**32**), CuCl, Et_2O, 0°C.

Figure 64. Feringa's ECA's reported conditions using Grignard reagents.

Table 5. Validating the reaction conditions using Grignard reagents reported by Feringa.

Entry	Catalyst	T (°C)	t (h)	Cu Salt	Solvent	Yield (%)	ee[a]
1	--	0	2	CuCl	Et_2O	80	0[a]
2	**32**	0	2	CuCl	Et_2O	77	89[a]

[a]ee determined by chiral GC analysis (CyclodexB).

Feringa's reaction results of 83% yield and 90% ee were successfully repeated (Table 5, Entry 2). The reactions were performed on 100 mg scale and the products were purified by thin layer chromatography. Attempts to purify using distillation were unsuccessful due to the similarity in boiling points of compounds **3** and **31**. The enantioselectivity of the reaction (Table 5, Entry 2) was measured by gas chromatography (GC) using a chiral column. The peaks of the GC chromatogram (Figure 65) were integrated and substituted into the formula **A.1** to establish an enantioselectivity value.

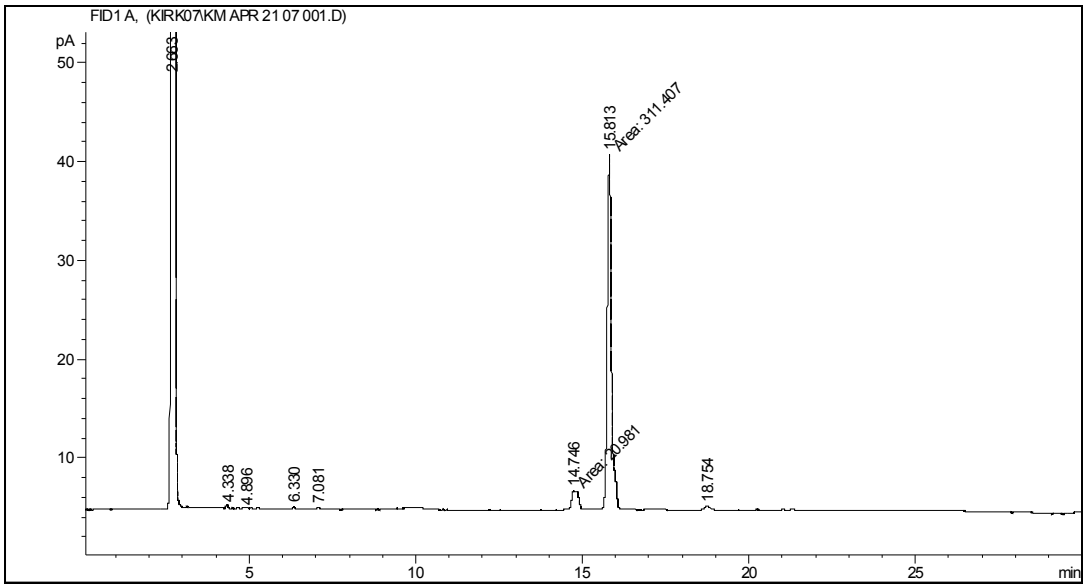
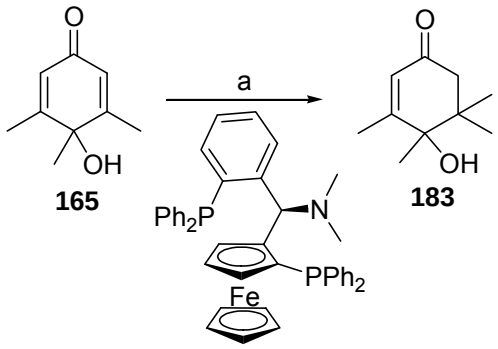


Figure 65. GC chromatogram using a chiral column of product **31** from a MeMgBr Grignard addition reaction to compound **3** with Taniaphos.

After validating the reaction conditions published by Feringa, the same conditions were applied to **165** (Figure 66). The results are summarized in Table 6.



a) MeMgBr, Taniaphos (**32**), CuCl, Et_2O, 0°C.

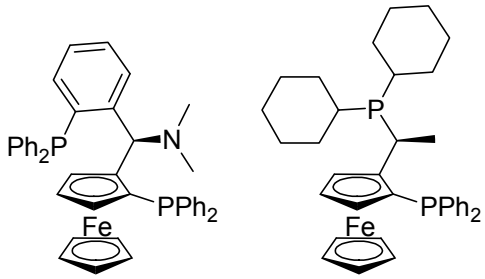
Figure 66. Grignard reaction using conditions reported by Feringa to **165**.

Table 6. Grignard reaction using conditions reported by Feringa to **165**.

Entry	Catalyst	T (°C)	t (h)	Cu Salt	Grignard	Solvent	Yield (%)	ee[a]
1	**32**	0	2	CuCl	MeMgBr	Et_2O	72	3[a]
2	**32**	0	2	CuCl	MeMgBr	THF	70	3[a]
3	**32**	-78	2	CuBr·SMe_2	MeMgBr	THF	88	3[a]
4	**32**	-78	2	CuBr·SMe_2	MeMgBr	PhMe	54	3[a]

[a]ee determined by chiral HPLC analysis ((R,R)-Whelk-(O,1)).

Compound **165** was alkylated in modest yields to obtain compound **183**. Unfortunately, poor enantiomeric excess was observed. Only 3% ee was observed for the reaction (Table 6, Entry 1) that utilized the same conditions as the conditions published by Feringa. Reactions with highly reactive Grignard reagents are sometimes faced with problems such as fast uncatalyzed side reactions and the presence of competing chiral and achiral copper complexes in solution.[51] The low enantioselectivities observed demonstrated that the racemic or uncatalyzed reaction was dominating or that the ligand did not impart selectivity. Although a mechanism for enantioselective conjugate addition to cyclic enones with a Taniaphos ligand is unknown, a mechanism for enantioselective conjugate addition to acyclic enones with a Josiphos ligand has been proposed. Josiphos is a similar ferrocene-based ligand (Figure 67) that has been found to be the ligand of choice for enantioselective conjugate addition reactions to acyclic enones.[132]



Taniaphos 32 **Josiphos 189**

Figure 67. Ferrocene-based ligand structures.

The Josiphos ligand has been shown to be highly efficient at forming copper complexes, which avoids the presence of free copper salts that could promote the uncatalyzed racemic reaction. The acyclic ECA mechanism using Josiphos (Figure 68) has been thoroughly explored and supported by kinetic, spectroscopic, and electrochemical analysis.[132]

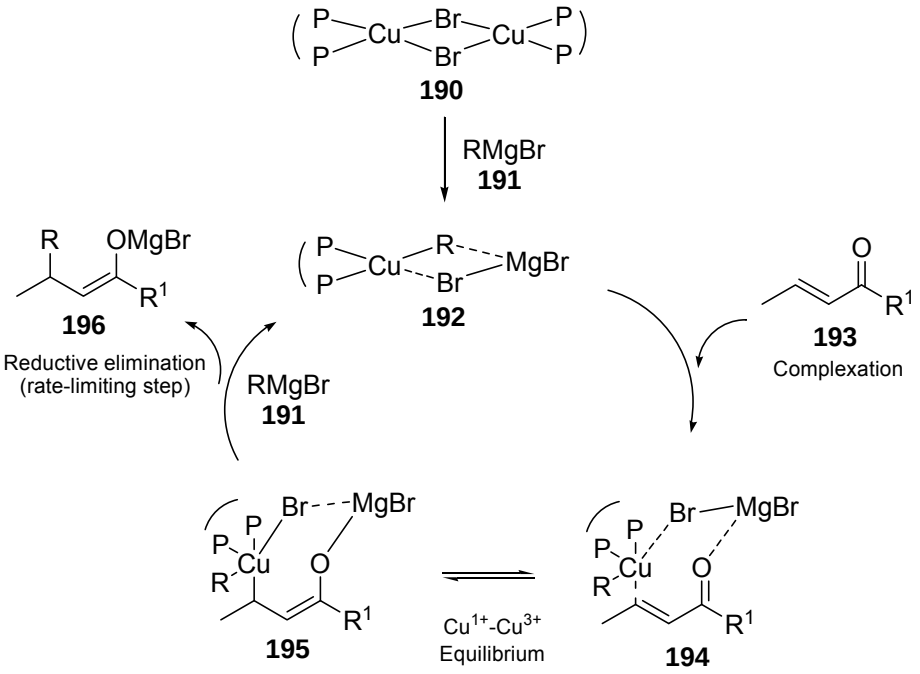


Figure 68. Acyclic ECA mechanism using Josiphos.

The monomeric complex **192**, formed by the transmetalation of the dimeric Josiphos complex **190** by a Grignard reagent **191**, was identified as the active catalytic species.[133] The π complexation of **192** to the substrate leads to a fast equilibrium involving a Cu^{+1} π complex and Cu^{+3} σ complex, which is followed by the rate-limiting reductive-elimination step to afford the magnesium enolate of the final product.[132] Although this was not a demonstrated mechanism for enantioselective conjugate addition using Taniaphos, the ligand structures of Taniaphos and Josiphos were similar. It was then assumed that these ligands followed similar reaction mechanisms. As a result, the equilibrium step or transition state **194** was modeled using compound **165** and Taniaphos (Figure 69). In addition, the transition state **194** was also modeled using Taniaphos and the successful result, compound **3** (Figure 70). The modeled transition state **194** using compound **165** indicated that there was a possible steric interaction between the β-methyl substituent of compound **165** and the two phenyl rings of the Taniaphos ligand. However, in the case of the modeled transition state **194** using compound **3** there was no indication of a steric interaction due to the absence of a β-methyl substituent.

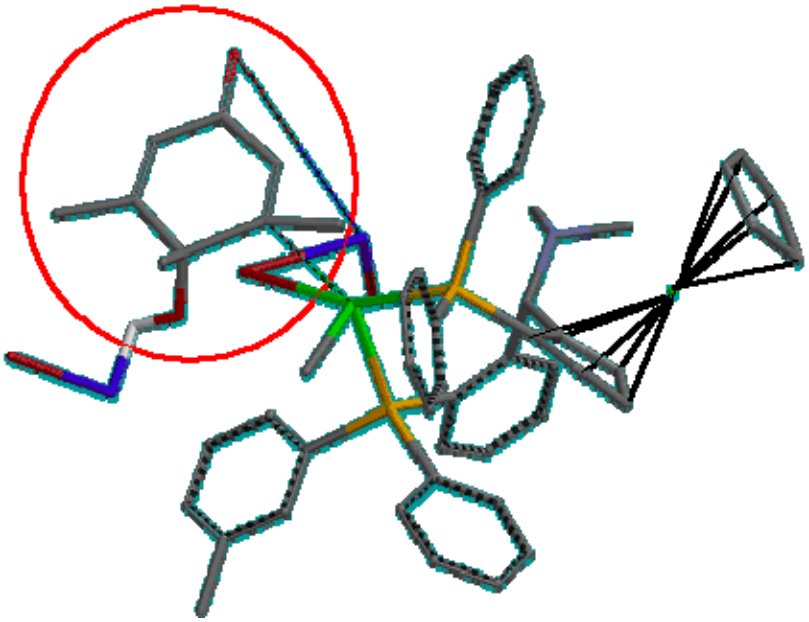


Figure 69. Modeled transition state **194** using compound **165** and Taniaphos.

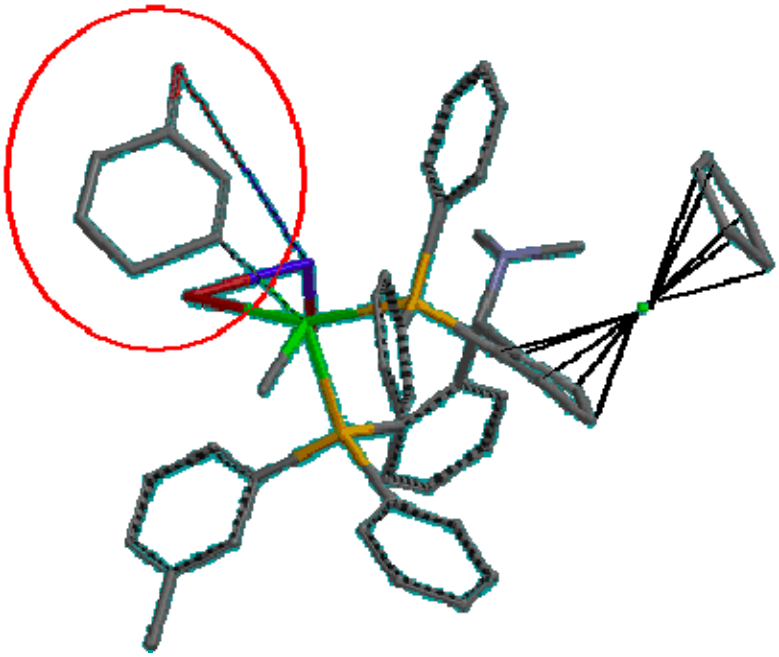


Figure 70. Modeled transition state **194** using compound **3** and Taniaphos.

Variables such as temperature, Cu salt and solvent (Table 6, Entries 2, 3 and 4) were altered in order to try to increase the enantioselectivity of the reaction and perhaps relieve a possible steric interaction. Reactions (Table 6, Entries 1, 2, 3 and 4) afforded similar isolated yields in both strong non-coordinating solvents and

weak non-coordinating solvents. However, in the case of PhMe there was a reduction in the yield of the reaction. This observation is contrary with later work done by Feringa[134] where weak non-coordinating solvents were replaced by stronger non-coordinating solvents in order to increase yields. It is well understood that the polarity and Lewis basicity of the solvent can significantly affect the aggregation of the Grignard reagent species in solution.[135] Solvent effects are usually explained by the Lewis basicity of the solvent. The THF solvent assists in an addition reaction by acting as a sterically demanding coordinating agent. Thus, the higher Lewis basicity of THF forces it to form a more rigid complex with the Grignard reagent. However, Et_2O possesses a lower Lewis basicity which results in a less rigid complex and in turn a less sterically demanding coordinating agent.[136] Although Et_2O should result in less aggregation and consequently higher yields, this is not the case for this reaction. The importance of the Cu salt (Table 6, Entries 2 and 3) was shown as the yield of the reaction was augmented significantly with the addition of $CuBr{\cdot}SMe_2$. The result in entry 3 produced an 18% increase in yield in comparison to Entry 2. Cu^{+1} salt are known to have a 1,4-directing effect when used with Grignard reagents.[137] In addition, it has also been demonstrated that Cu salt-free conjugate addition reactions may be slower[138] than other organocopper complexes or even totally inactive.[139] Thus, this is in agreement with our observation that higher yields can be obtained in the presence of a Cu salt.

Grignard addition to **165** was facially diastereoselective and the hydroxyl moiety seemed to be assisting the addition. As a result, it was hypothesized that ethers or protected hydroxyl substituents would behave in the same manner by providing coordination from the oxygen atom. Thus, the hydroxyl moiety of **165** was protected as methoxy (OMe), methoxy methyl (MOM) and methoxyethoxy methyl (MEM) ethers (Figure 71). Lastly, it was thought that if a conjugate addition reaction to an ether substrate was successful, the ether substituent could be altered into a chiral ether substituent that would in turn lead to a diastereoselective reaction.

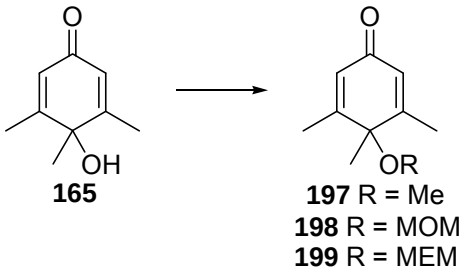
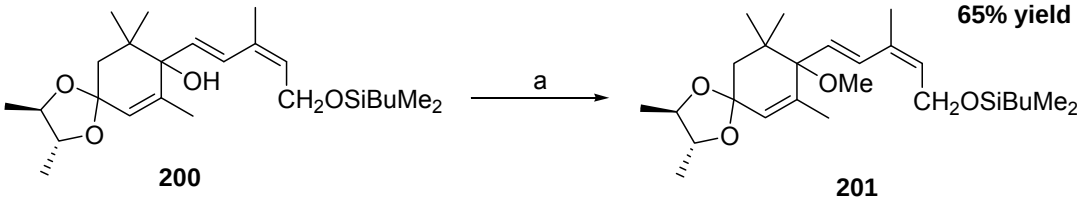


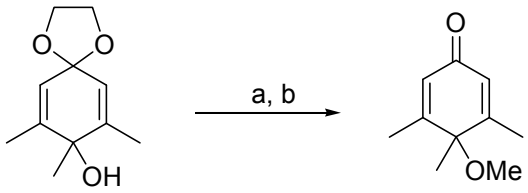
Figure 71. Synthesis of ethers.

The methyl ether **197** was synthesized using a method adapted from the synthesis of a methoxy-trimethylcyclohexenone derivative **201** by Abrams (Figure 72).[140] Compound **174** was used as starting material. The free alcohol group was reacted with one equivalent of methyllithium to form a lithium salt. The lithium salt was then alkylated with methyl iodide and the ketal functionality was removed with 10% hydrochloric acid to give compound **197** in a 60% yield (Figure 73). Camps[141] reported the synthesis of compound **197** in a 56% yield via an oxidation reaction in MeOH of 3,4,5-trimethylphenol with iodobenzene diacetate. The known structure of compound **197** was then confirmed by ^{1}H and ^{13}C NMR. The ^{1}H NMR spectrum displayed four singlet peaks at 6.13 ppm, 2.92 ppm, 1.97 ppm and 1.35 ppm (Figure 74). The peak at 6.13 ppm represented the two olefinic protons (HC-2, HC-6) (Table 7, Entry 1). The methyl ether group protons were represented by the peak at 2.92 ppm (H_3C-10) (Table 7, Entry 2). The vinyl methyl group protons (H_3C-7, H_3C-9) (Table 7, Entries 3) were found to be represented by a peak at 1.97 ppm. The remaining methyl group protons (H_3C-8) (Table 7, Entries 4) were found to be the one remaining peak at 1.35 ppm. The ^{13}C NMR spectrum further supported the structure by revealing seven peaks representing the correct number of magnetically nonequivalent carbons.



a) MeLi, MeI, THF, -78°C→RT.

Figure 72. Abrams synthesis of a methoxy-trimethylcyclohexenone derivative **201**.



a) MeLi, MeI, THF, -78°C→RT. b) 10% HCl, THF, RT.

Figure 73. Synthesis of compound **197**.

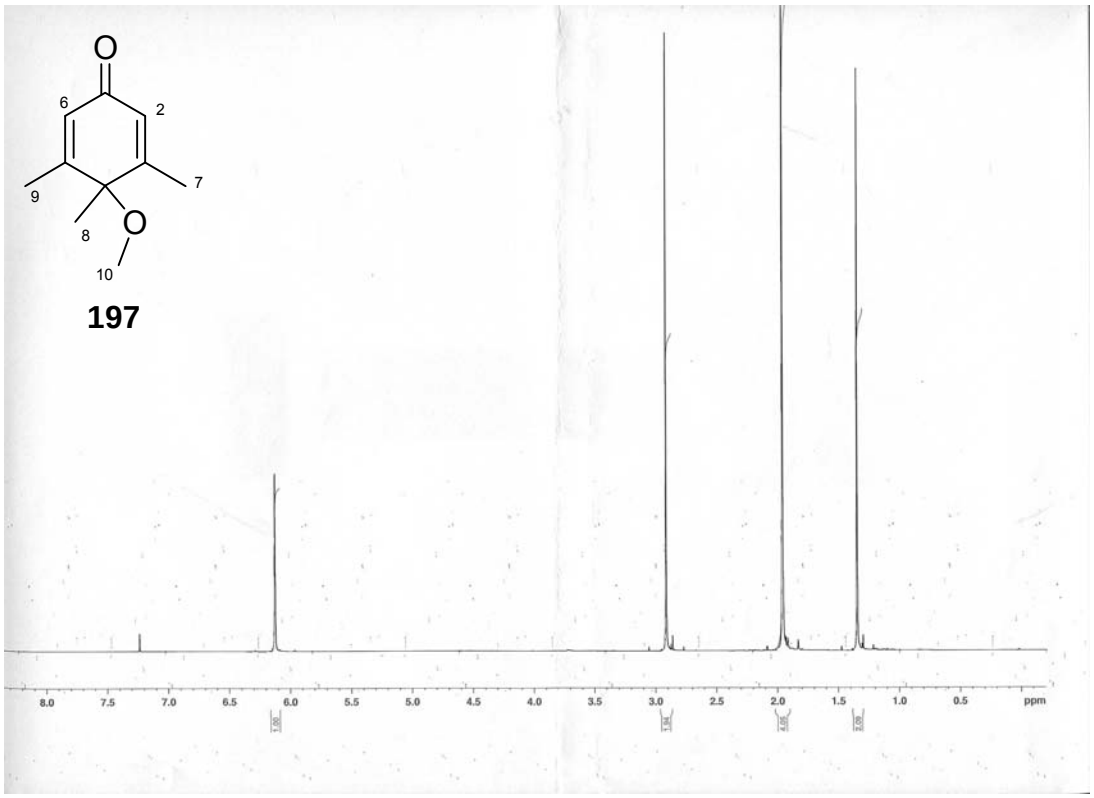
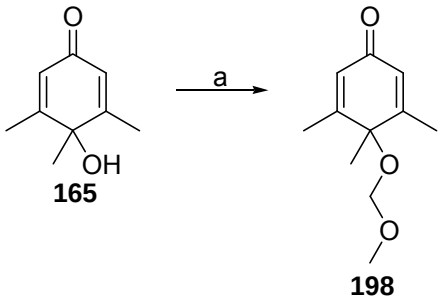


Figure 74. ^{1}H NMR spectrum of compound **197**.

Table 7. Chemical shifts of the ^{1}H NMR spectrum of compound **197**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-2, HC-6	6.13	2H, s
2	H_3C-10	2.92	3H, s
3	H_3C-7, H_3C-9	1.97	6H, s
4	H_3C-8	1.35	3H, s

The methoxymethyl ether **198** was synthesized using a method reported by Narasaka[142] which facilitates the protection of tertiary alcohols. The MOMCl was treated with NaI in a Finkelstein reaction to produce a more reactive species MOMI. Next, compound **165** was combined with the newly formed reactive intermediate, DIPEA and DME. The solution was refluxed for twelve hours to produce compound **198** in 78% yield (Figure 75). Compound **198** was structurally characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and UV. The ^{1}H NMR spectrum depicted 5 peaks at 6.11 ppm, 4.33 ppm, 3.39 ppm, 2.04 ppm and 1.42 ppm (Figure 76). The singlet peak at 6.11 ppm (Table 8, Entry 1) represented the olefinic (HC-2, HC-6) protons. The MOM alkyl group protons (H_2C-10, H_3C-11) were depicted by two singlet peaks at 4.33 ppm and 3.39 ppm (Table 8, Entries 2 and 3). The vinyl methyl group (H_3C-7, H_3C-9) (Table 6, Entry 4), and the remaining methyl group (H_3C-8) (Table 8, Entry 5) protons were found to be represented by singlet peaks at 2.04 ppm and 1.42 ppm, respectively. The ^{13}C NMR spectrum further supported the structure by revealing 8 peaks representing the correct number of magnetically nonequivalent carbons. The IR spectrum revealed the presence of a carbonyl stretch at 1674 cm^{-1} and an α,β-unsaturated carbonyl stretch at 1635 cm^{-1}. Further evidence was obtained from the electron impact mass spectrum, where the molecular ion peak was found to be 196.1107 (calc. 196.1107). Lastly, the UV spectrum of **198** produced a single absorption at 236 nm and an extinction coefficient of 1.6 x 10^{4} $M^{-1}\cdot cm^{-1}$ which is comparable to the known literature values of a similar *p*-dienone structures.[131]



a) MOMCl, NaI, DIPEA, DME Reflux, 12 h.

Figure 75. Synthesis of compound **198**.

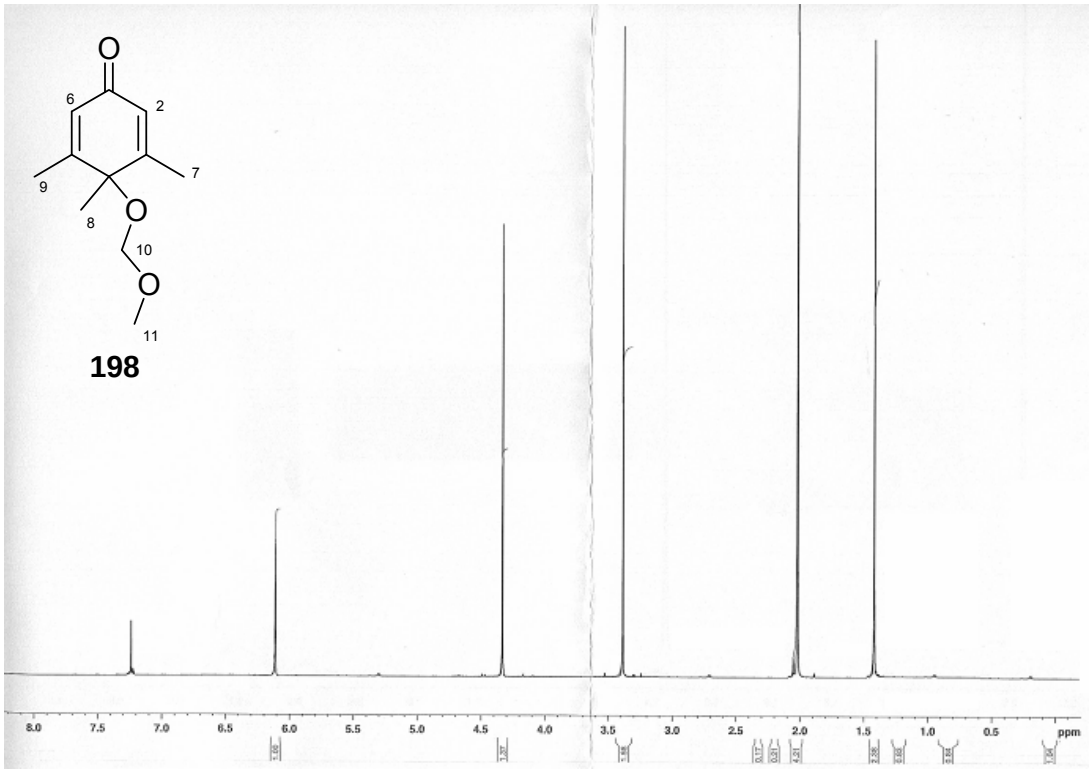
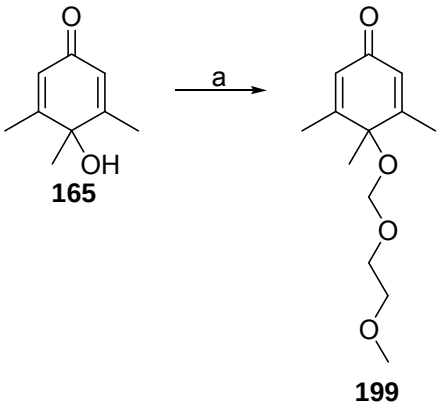


Figure 76. ^{1}H NMR spectrum of compound **198**.

Table 8. Chemical shifts of the ^{1}H NMR spectrum of compound **198**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-2, HC-6	6.11	2H, s
2	H_2C-10	4.33	2H, s
3	H_3C-11	3.39	3H, s
4	H_3C-7, H_3C-9	2.04	6H, s
5	H_3C-8	1.42	3H, s

The methoxyethoxy methyl ether **199** was synthesized using a method reported by Corey.[143] The method involved treating compound **165** with MEMCl and DIPEA in DCM at room temperature for three hours. As a result, the reaction produced compound **199** in a moderate 48% yield (Figure 77). Compound **199** was structurally elucidated by ^{1}H NMR, ^{13}C NMR, IR, MS and UV. The ^{1}H NMR spectrum demonstrated 7 peaks at 6.06 ppm, 4.39 ppm, 3.66 ppm, 3.46 ppm, 3.29 ppm, 2.04 ppm and 1.37 ppm (Figure 78). The singlet peak at 6.06 ppm (Table 9, Entry 1) represented the olefinic (HC-2, HC-6) protons. The vinyl methyl protons (H_3C-7, H_3C-9) (Table 9, Entry 6), and the remaining methyl group protons (H_3C-8) (Table 9, Entry 7) were found to be represented by singlet peaks at 2.04 ppm and 1.37 ppm, respectively. The alkyl protons in the MEM functionality were found two be represented by a singlet peak at 4.39 ppm (H_2C-10) (Table 9, Entry 2), two triplet peaks at 3.66 ppm (H_2C-12) (Table 9, Entry 3) and 3.46 ppm (H_2C-11) (Table 9, Entry 4), and another singlet peak at 3.29 ppm (H_3C-13) (Table 9, Entry 5). The ^{13}C NMR spectrum further supported the structure by revealing 10 peaks representing the correct number of magnetically nonequivalent carbons. The IR spectrum revealed the presence of a carbonyl stretch at 1671 cm^{-1} and an ether stretch at 1072 cm^{-1}. Further proof was attained from the chemical ionization mass spectrum, where the protonated molecular ion peak was found to be 241.1439 (calc. 241.1439). Lastly, the UV spectrum of **199** produced a single absorption at 236 nm and an extinction coefficient of 2.0 x 10^4 $M^{-1}\cdot cm^{-1}$ which is comparable to the known literature values of a similar *p*-dienone structures.[131]



a) MEMCl, DIPEA, CH_2Cl_2, 25°C, 3h.

Figure 77. Synthesis of compound **199**.

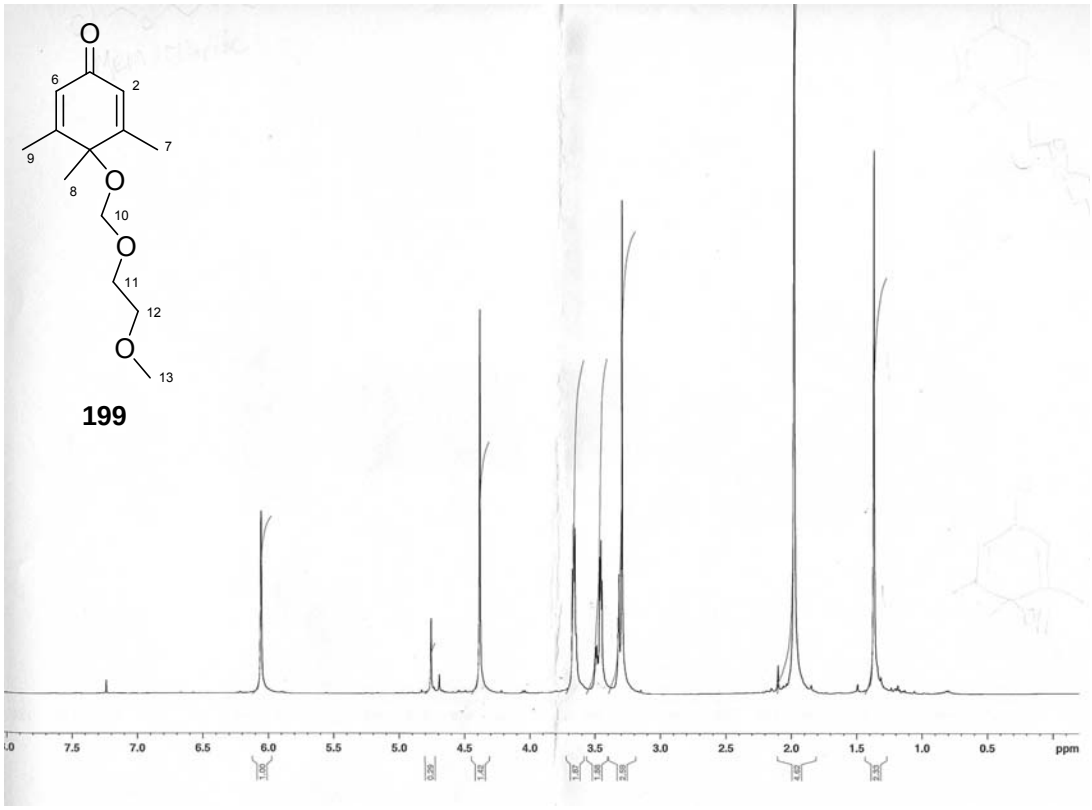
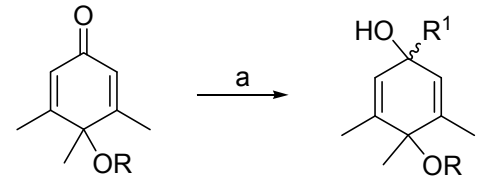


Figure 78. ^{1}H NMR spectrum of compound **199**.

Table 9. Chemical shifts of the ^{1}H NMR spectrum of compound **199**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-2, HC-6	6.06	2H, s
2	H_2C-10	4.39	2H, s
3	H_2C-12	3.66	2H, t, J = 4.7
4	H_2C-11	3.46	2H, t, J = 4.8
5	H_3C-13	3.29	3H, s
6	H_3C-7, H_3C-9	2.04	6H, s
7	H_3C-8	1.37	3H, s



197 R = Me
198 R = MOM
199 R = MEM

202 R = Me
203 R = MOM
204 R = MEM

a) R^1MgBr, THF, -78°C.

Figure 79. Grignard addition to ethers **202**, **203** and **204**.

Table 10. Grignard addition reaction to **197**, **198** and **199**.

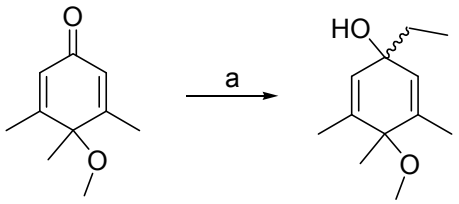
Entry	Ether	1,2-addition	Cu Salt	Grignard	Yield (%)[a]
1	**197**	**202**	--	EtMgBr	74
2	**197**	**202**	CuCl	EtMgBr	90
3	**198**	**203**	--	EtMgBr	73
4	**198**	**203**	CuCl	EtMgBr	85
5	**199**	**204**	--	MeMgBr	78

[a]isolated yields.

The newly formed ether products, **197**, **198** and **199**, were submitted to a Grignard addition reaction (Figure 79 and 80). The results are summarized in Table 10. However, unlike compound **165**, compounds **197**, **198** and **199** reacted with a Grignard reagent to produce a mixture of 1,2-addition diastereomeric products. The methyl and MOM ether products produced a diastereomeric ratio of approximately ~1:7. The MEM ether product produced a diastereomeric ratio of approximately ~1:1.5. Coordination from the oxygen atom to produce a facially selective 1,4 addition product was not observed. The comparison of the diastereomeric ratios

suggested that coordination from the oxygen to produce a facially selective 1,2 addition product is also not observed and that the 1,2 addition reaction was governed by the size of the ether. Organometallic reagents[144] have been shown to react with γ-substituted α,β-unsaturated carbonyl compounds to produce 1,2-addition products. In particular, Grignard reagents have been shown to react with the substrate 4,4-dimethyl-2-cyclohexen-1-one to produce a 1,2 addition product. The reasoning for this 1,2 addition (Table 10, Entries 2 and 4) was thought to be due to steric effects by the two methyl groups bonded to the γ-position of the cyclohexen-1-one ring and due to the absence of the hydroxyl moiety assisting the reaction. Thus, in this study, protecting the hydroxyl group of compound **165** and converting it to an ether functionality increased the size of the substituent. This increase in size resulted in an increase in steric bulk at the γ-position of compounds **197**, **198** and **199**. Therefore, the increase in steric bulk may have sheltered the β reaction sites of compounds **197**, **198** and **199** to produce the 1,2 addition products **202**, **203** and **204**.

Entries 2 and 4 in Table 10 were reactions that made use of a Cu salt. Consequently, the yields of the reactions were increased by 10-15%. The use of Cu salts in combination with Grignard reagents to increase yields is precedented.[144] The Cu salts act as coordinating agents to Grignard reagents. In turn, the reactivity as well as the regioselectivity of Grignard reagent coordinated species is increased.[144] However, in this study, the β reaction sites of compounds **197**, **198** and **199** seemed to be sterically sheltered by the γ substituents. As a result, the copper-modified Grignard reagents were directed towards the less hindered carbonyl functionality resulting in 1,2 addition products **202**, **203** and **204**. Finally, this increased reactivity by the Cu salt must account for this increase in yield.



a) EtMgBr, THF, -78°C.

Figure 80. Grignard addition reaction to **202**.

The mixture of diastereomeric products **202** was structurally characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and UV. The ^{1}H NMR spectrum demonstrated 6 expected peaks for the major diastereomer at 5.56 ppm, 2.88 ppm, 1.73 ppm, 1.52 ppm, 1.22 ppm and 0.69 ppm. The singlet peak at 5.56 ppm represented the two olefinic (HC-2, HC-6) (Table 11, Entry 1) protons (Figure 81). The methyl ether protons (H_3C-12) (Table 11, Entry 2) were found to be represented by the singlet peak at 2.88 ppm. The vinyl methyl (H_3C-9, H_3C-11) (Table 11, Entry 3), and the remaining methyl (H_3C-10) (Table 11, Entry 5) protons were found to be represented by two singlet peaks at 1.73 ppm and 1.22 ppm, respectively. The remaining ethyl group (H_2C-7, H_3C-8) (Table 11, Entries 4 and 6) protons were represented by the quartet and triplet peaks at 1.52 ppm and 0.69 ppm, respectively. The ^{13}C NMR spectrum supported the structure of the mixture of diastereomers **202** by revealing 9 major peaks representing the correct number of magnetically nonequivalent carbons. For example, the spectrum demonstrated 4 peaks at 137.23 ppm (C-3', C-5'), 131.03 ppm (C-2', C-6'), 75.24 ppm (C-4') and 69.76 ppm (C-1'), representing the 6 carbon ring structure. The ^{13}C NMR spectrum also showed 2 peaks at 34.04 ppm and 8.72 ppm, representing the ethyl group (C-7', C-8') carbon atoms. The remaining peaks in the spectrum at 50.89 ppm, 24.38 ppm and 16.98 ppm represented the methyl ether carbon (C-12'), the methyl carbon (C-10') and the vinyl methyl carbons (C-9',C-11'), respectively. The IR spectrum showed the presence of a hydroxyl stretch at 3423 cm^{-1} and an ether stretch at 1066 cm^{-1}. Further proof was attained from the electron impact mass spectrum where a fragment ion peak of 178.1356 (calc. 178.1356) was found. Lastly, the UV spectrum

of **202** portrayed a single absorption at 204 nm with an extinction coefficient of 1.4 x 10^4 $M^{-1}\cdot cm^{-1}$ $M^{-1}\cdot cm^{-1}$ which is in agreement with the literature value of alkenes.[131]

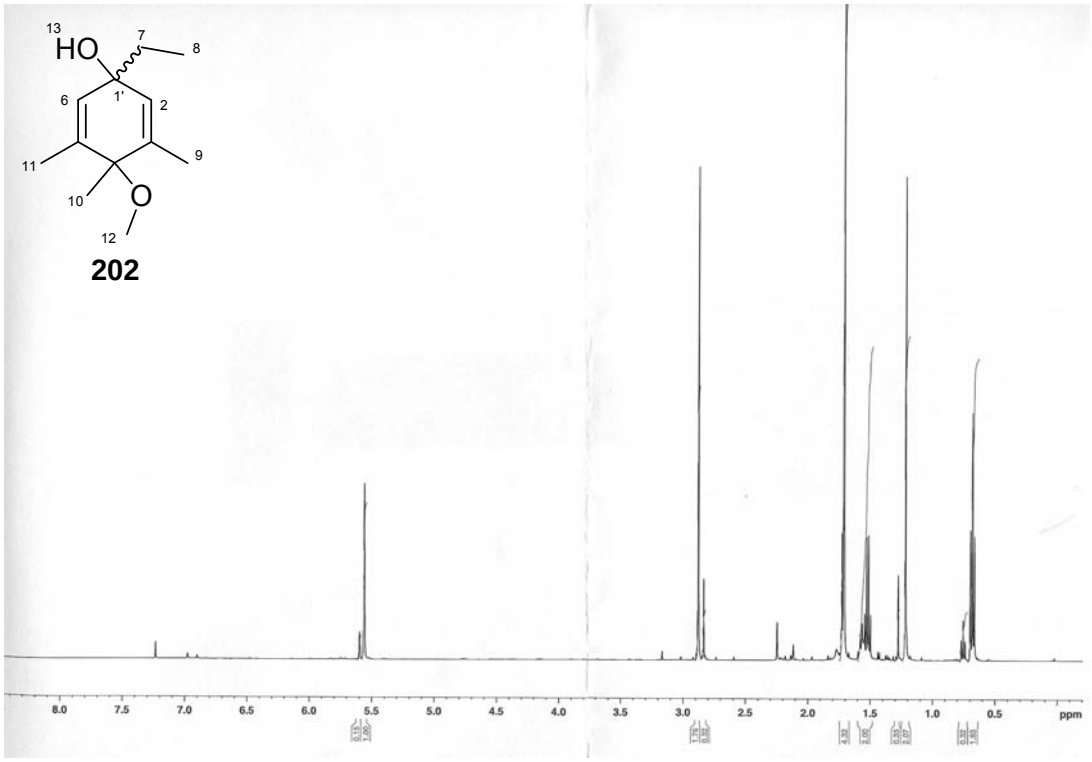


Figure 81. ^{1}H NMR spectrum of compound **202**.

Table 11. Chemical shifts of the ^{1}H NMR spectrum of compound **202**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-2, HC-6	5.56	2H, s
2	H_3C-12	2.88	3H, s
3	H_3C-9, H_3C-11	1.73	6H, s
4	H_2C-7	1.52	2H, q, J = 7.5
5	H_3C-10	1.22	3H, s
6	H_3C-8	3.29	3H, t, J = 7.5

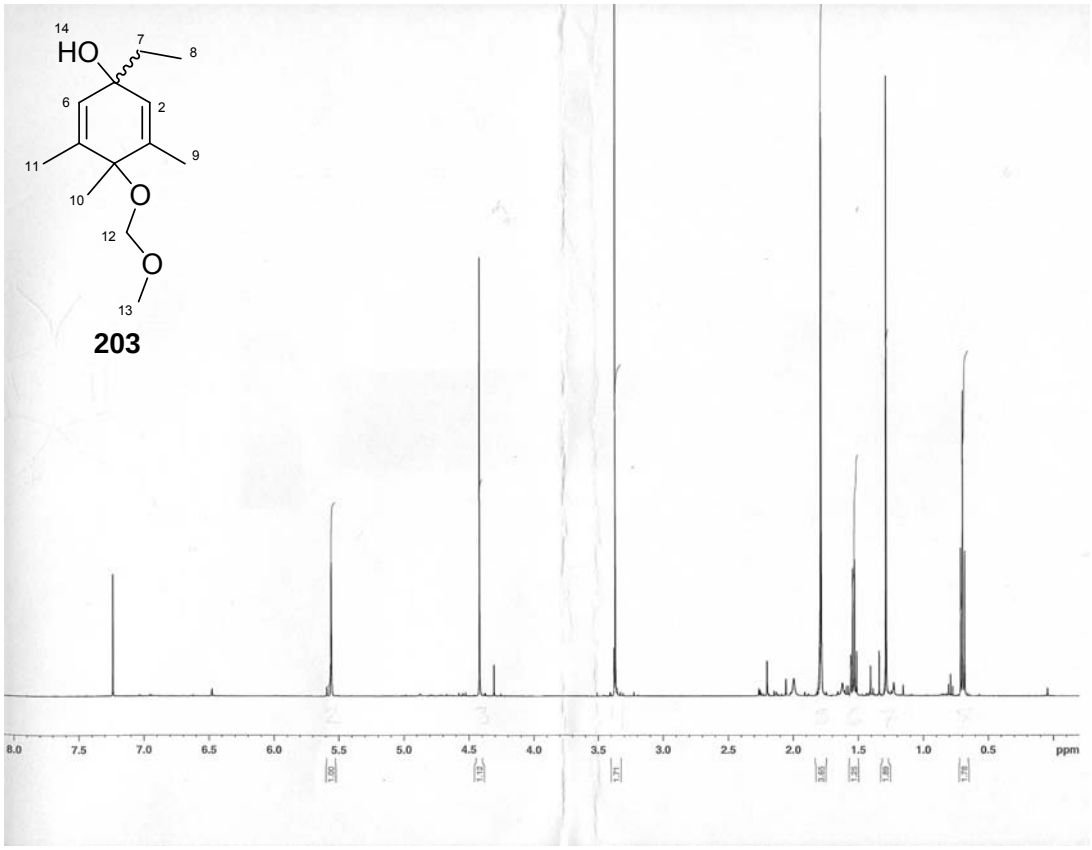


Figure 82. ^{1}H NMR spectrum of compound **203**.

Compounds **203** and **204** possessed similar structural data to the diastereomeric mixture compound **202**. Compounds **203** and **204** were also diastereomeric mixtures, however, a few differences were found in their ^{1}H NMR spectra. Compound **203** had an extra proton signal at 4.42 ppm (H_2C-12) in its ^{1}H NMR spectrum (Figure 82). The proton signal represented the two CH_2 protons in the MOM protection group. Compound **204** also had extra proton signals at 4.51 ppm, 3.66 ppm and 3.50 ppm (H_2C-11, H_2C-13, H_2C-12) (Figure 83). These proton signals represented the 6 CH_2 protons in the MEM protection group. In addition, the addition reaction to compound **204** was performed with a methyl Grignard reagent thus, the appearance of an extra methyl group at 1.19 ppm (H_3C-7). The remaining ^{13}C NMR, IR, MS and UV characterization data further confirmed the synthesis of compounds **203** and **204**.

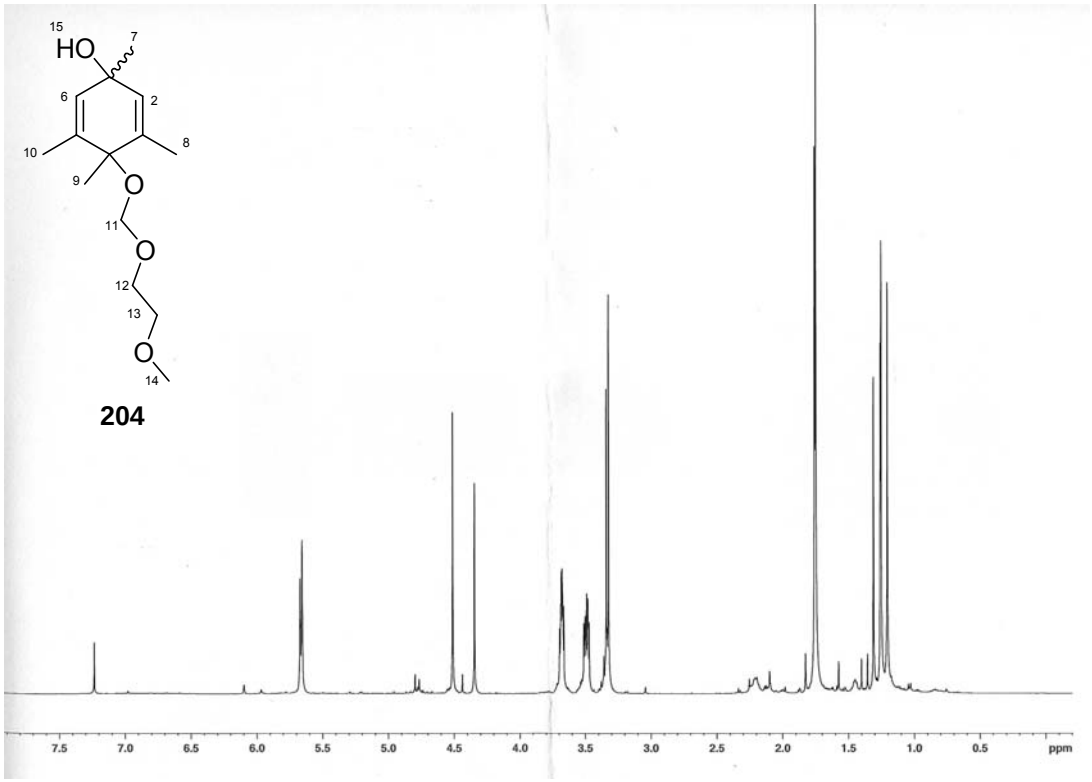
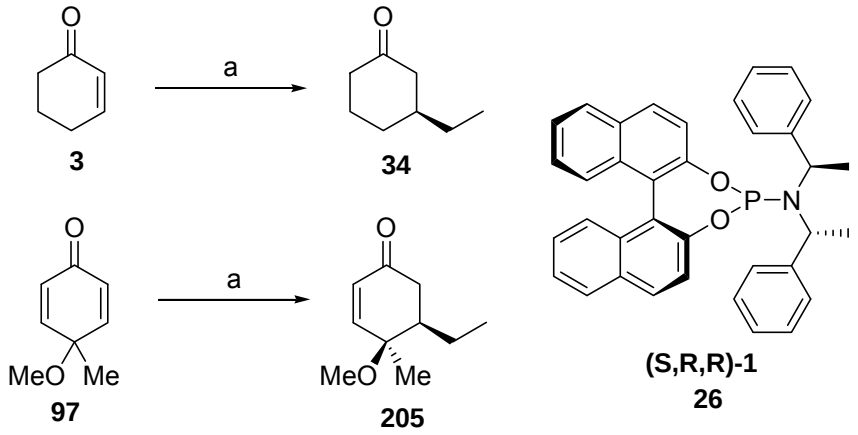


Figure 83. ^{1}H NMR spectrum of compound **204**.

2.1.3 Dialkylzinc Conjugate Additions.

The use of dialkylzinc reagents to perform conjugate addition reactions is precedented[75]. ECA of dialkylzinc reagents to simple cyclic enones has been previously reported by Feringa. As a result, an effort to repeat the reported reaction conditions by Feringa commenced. The results are summarized in Table 12. The reaction involved dialkylzinc reagents, 2-cyclohexen-1-one **3** and a phosphoramidite ligand **26** (Figure 84).



a) Et_2Zn, $Cu(OTf)_2$, (S,R,R)-1 (**26**), PhMe, -30°C.

Figure 84. Feringa's ECA reported conditions using dialkylzinc reagents.

Table 12. Validating the reaction conditions using dialkylzinc reagents reported by Feringa.

Entry	Catalyst	T (°C)	Dialkylzinc Reagent	Solvent	Yield (%)	ee[a]
1	--	-30	Et_2Zn	PhMe	94	0[a]
2	--	-30	Me_2Zn	PhMe	NR	--
3	**26**	-30	Et_2Zn	PhMe	90	85[a]

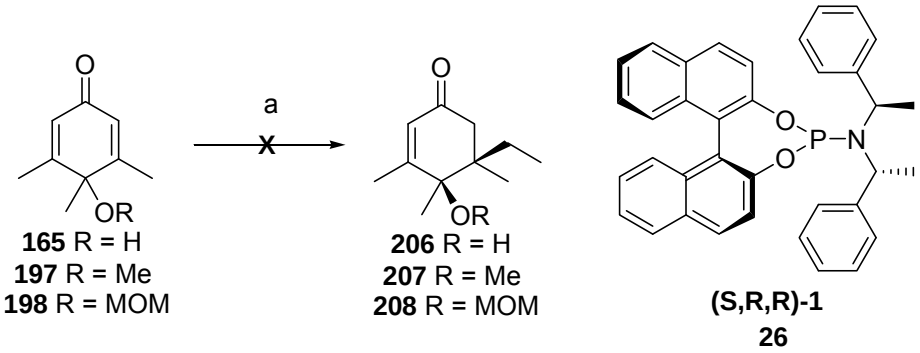
[a]ee determined by chiral GC analysis (CyclodexB).

Feringa's reaction conditions were successfully repeated in Table 12, Entry 3. A yield of 90% was achieved which is comparable to Feringa's yield of 94%. However, the enantioselectivity obtained was slightly lower than the enantiomeric excess of >98% reported by Feringa. The slight drop in enantioselectivity may be a result of the dryness of the conditions. It has been reported that the addition of more than 1.0 mol% of water results in a dramatic decrease in enantioselectivity and chemical yield.[145]

The effects of different alkylzinc reagents were also tested (Table 12, Entry 2) where Me_2Zn was used instead of Et_2Zn. Dimethylzinc was attempted because ideally the target of this project was to add a methyl group to **165**. However, after 24 hours there was no reaction between 2-cyclohexen-1-one **3** and Me_2Zn. Me_2Zn

is known to be ten times less reactive than Et_2Zn[61]. As a result, reactions involving Me_2Zn may require higher reaction temperatures and longer reaction times[61].

After validating the dialkylzinc reaction conditions published by Feringa, the conditions were applied to **165** (Figure 85). It was anticipated that the addition of methyl groups at the 3 and 5 positions would not affect the addition reaction. The results are summarized in Table 13.



a) Et_2Zn, $Cu(OTf)_2$, (S,R,R)-1 (**26**), PhMe, -30°C.

Figure 85. Dialkylzinc reaction using conditions reported by Feringa to **165**.

Table 13. Dialkylzinc reaction using conditions reported by Feringa to **165**.

Entry	Enone	T (°C)	t (h)	Cu Salt	Dialkylzinc Reagent	Yield (%)	ee
1	**165**	Gradient[a]	24	$Cu(OTf)_2$	Et_2Zn	NR	--
2	**165**	Gradient[a]	24	$Cu(OTf)_2$	Me_2Zn	NR	--
3	**165**	Gradient[a]	24	$Cu(OTf)_2$	2_{eq} Et_2Zn	NR	--
4	**165**	Gradient[a]	24	$Cu(OTf)_2$	1_{eq} MeLi 1_{eq} Et_2Zn	NR	--
5	**197**	Gradient[a]	24	$Cu(OTf)_2$	Et_2Zn	NR	--
6	**197**	Gradient[a]	24	$Cu(OTf)_2$	2_{eq} Et_2Zn	NR	--
7	**198**	Gradient[a]	24	$Cu(OTf)_2$	Et_2Zn	NR	--
8	**198**	Gradient[a]	24	$Cu(OTf)_2$	2_{eq} Et_2Zn	NR	--

[a]The initial temperature for all reactions was –78°C and if no reaction was observed after 3 hours then the temperature was raised every 2 hours in 20°C increments to reflux.

Unfortunately no reaction was observed between compound **165** and dialkylzinc reagents. Conditions such as temperature and equivalents of dialkylzinc reagent were altered, however, no product formation was ever observed. The presence of the hydroxyl moiety of compound **165** was hypothesized to be the cause of the lack in reactivity. Feringa's work made use of cyclohexadienone **97**. As a

result, dialkylzinc reactions were performed using protected ethers compounds **197** and **198**. Again, no reaction was observed. Lastly, no reaction was observed when excess equivalents of dialkylzinc and temperature elevation were combined with compounds **197** and **198**. Compound **197** is similar to compound **93**, but possesses methyl groups at the 3 and 5 positions. These methyl substituents at the β positions of the molecule must add an increased steric requirement for alkylzinc reagents to overcome.

Conjugate addition of dialkylzinc reagents to β-substituted enones has been reported by Hoveyda.[84] The β-substituted enone, compound **75** was synthesized using an allylic oxidation reaction reported by Catino.[146] Catino's reaction involved treating compound **209** with TBHP and $Rh_2(cap)_4$ in DCM at room temperature for one hour. As a result, the method produced compound **75** in a high 90% yield which was comparable to the 92% yield achieved by Catino (Figure 86).

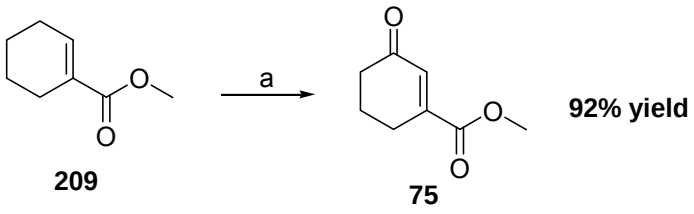
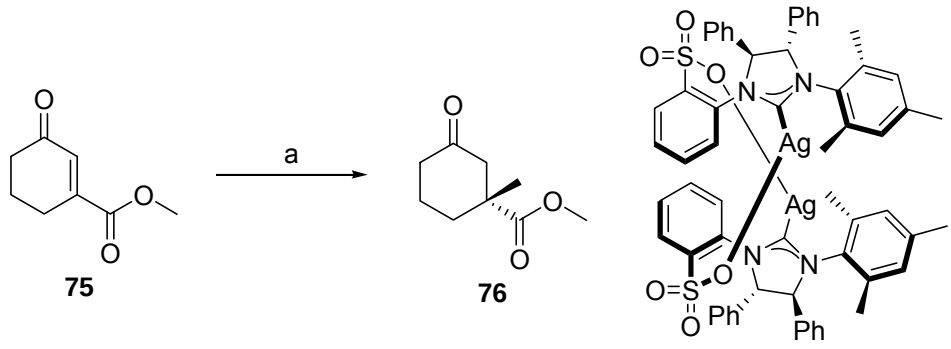


Figure 86. Synthesis of compound **75** by Catino's allylic oxidation.

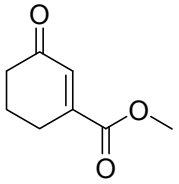
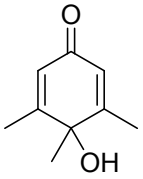
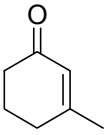
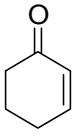
With compound **75** in hand, the reported reaction conditions by Hoveyda were repeated and validated. The results are summarized in Table 14. The reaction reported by Hoveyda involved dimethylzinc reagents, cyclic β-keto ester **75** and a new chiral N-heterocyclic carbene (NHC) ligand **77** (Figure 87). Hoveyda's reaction conditions were successfully repeated in Table 14, Entry 1. The yield of 70% obtained was similar to Hoveyda's yield of 72%. In addition, the obtained enantioselectivity of 86% was exactly the same as the enantioselectivity reported by Hoveyda.



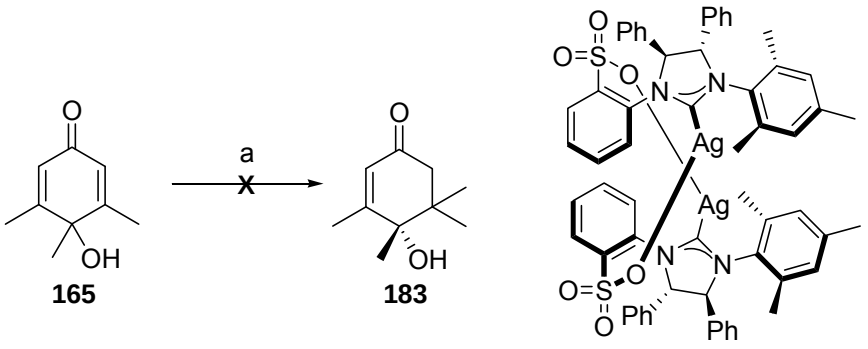
a) Me_2Zn, $Cu(OTf)_2.C_6H_6$, NHC-Ag Complex (**77**), tBuOMe, -30°C.

Figure 87. Hoveyda's ECAs reported conditions using dialkylzinc reagents.

Table 14. Reactions using dimethylzinc reagents reported by Hoveyda.

Entry	Enone	Yield (%)	ee[a]
1	 **75**	70	86
2	 **165**	NR	--
3	 **24**	NR	--
4	 **3**	NR	--

[a]ee determined by GC analysis (β-cyclodex).



a) Me_2Zn, $Cu(OTf)_2.C_6H_6$, NHC-Ag Complex (**77**), tBuOMe, -30°C.

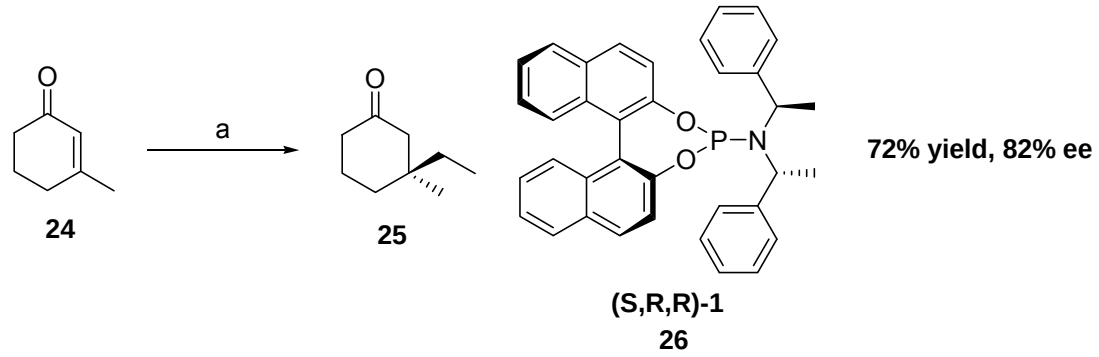
Figure 88. Dialkylzinc reaction using conditions reported by Hoveyda to **165**.

After validating the dimethylzinc reaction conditions published by Hoveyda, the conditions were applied to **165** (Figure 88). Unfortunately no reaction was observed between compound **165** and dimethylzinc (Table 14, Entry 2). As a result, the reaction was attempted with 3-methyl-2-cyclohexen-1-one **24** as well as 2-cyclohexen-1-one **3** in order to decide whether the β-keto ester functionality played a key role in this reaction. Again, no reaction was observed with substrates **24** and **3**. The β-keto ester seemed necessary for a reaction to occur. Hoveyda indicated that β-keto esters are activating functionalities.[84] In other words, the ester has an increased Lewis acidity which, in turn, activates or increases the Lewis basicity of the substrate.[147] As a result, the β-position of the substrate bearing the β-keto ester becomes more electrophilic. Thus, this increase in electrophilicity permits the dialkylzinc reagent to overcome the steric hindrance of a β-substituent.

2.1.4 Trialkylaluminum Conjugate Additions.

Enantioselective conjugate addition reactions that make use of organoaluminum reagents are precedented.[18] In 2005, Alexakis reported ECAs of alkylaluminum reagents to β,β-disubstituted cyclohexenones in the presence of a

phosphoramidite ligand **26** (Figure 89). An effort to repeat the published reaction conditions was then put forth. The results are summarized in Table 15.



a) Et_3Al, CuTC, (S,R,R)-1 (**26**), Et_2O, -30°C.

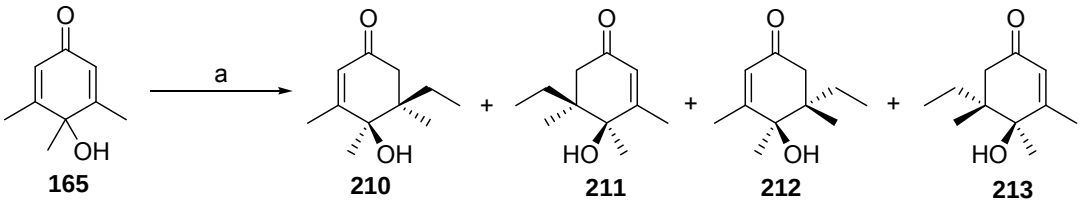
Figure 89. Alexakis' ECA reported conditions using trialkylaluminum reagents.

Table 15. Validating Alexakis' reaction conditions using trialkylaluminum reagents.

Entry	Catalyst	t (h)	Cu Salt	Dialkylzinc Reagent	Solvent	Yield (%)	ee
1	--	18	CuTC	Et_3Al	Et_2O	NR	--
2	**26**	18	CuTC	Et_3Al	Et_2O	70	81[a]

[a]ee determined by chiral GC analysis (β-cyclodex).

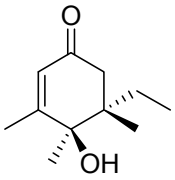
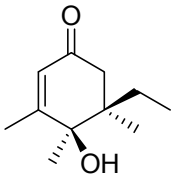
Alexakis' reported reaction conditions of 72% yield and 82 % ee were validated (Table 15, Entry 2). The yield and enantioselectivity achieved were comparable to Alexakis' results. In addition, in an attempt to make the racemate of **25**, it was also observed (Table 15, entry 1), that the reaction would not proceed without the presence of the chiral catalyst **26**. This lack of reactivity was also observed by Careno[90] where **165** was reacted with Me_3Al in the absence of a chiral auxiliary and no product was obtained. Despite the lower reactivity of trialkylaluminum reagents, Alexakis' published reaction conditions were applied to **165** (Figure 90). The results by Alexakis are summarized in Table 16.



a) Et_3Al, CuTC, (**26**), Et_2O, -15°C.

Figure 90. Trialkylaluminum reaction to **165** using conditions reported by Alexakis.

Table 16. Conjugate addition to **165** using Alexakis' reaction conditions.

Entry	T (°C)	dr[a]				Yield (%)
		 **-anti addition to OH**		 **-syn addition to OH**		
		(-)	**(+)**	**(-)**	**(+)**	
1	-30	--	--	--	--	NR
2	-15	7	17	16	60	15

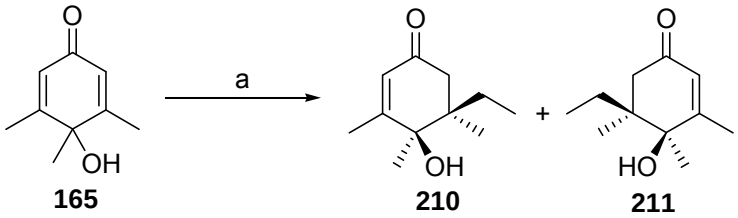
[a]dr determined by chiral HPLC analysis ((R,R)-Whelk-01).

Upon repeating the conditions reported by Alexakis, no reaction was observed (Table 16, Entry 1). However, when the temperature was raised to -15°C (Table 16, Entry 2) from -30°C compound **165** was successfully alkylated to produce a mixture of stereoisomeric compounds **210**, **211**, **212** and **213**. The yield obtained for the mixture of compounds **210**, **211**, **212** and **213** was low and modest enantioselectivities were observed.

2.1.4.1 Determination of the Syn Addition Compounds 210 and 211.

Compound **165** was reacted with ethylmagnesium bromide in a Grignard reaction to produce a standard for compounds **210** and **211**. Previous work with Grignard reagents demonstrated that Grignard reagents were assisted by the

alkoxide substituent of compound **165** to produce a diastereoselective product. In other words, the products of the reaction between ethylmagnesium bromide and compound **165** would be facially selective due to the hydroxyl moiety guiding the Grignard reagent to the same face of the molecule (Figure 91). The HPLC of the diastereomerically pure product displayed two peaks with a 1:1 integration ratio (Figure 50). The mixture of compounds **210** and **211** was separated by preparative HPLC. The ^{1}H NMR spectra of the isolated compounds were found to be identical (Figure 92).



a) Grignard addition reaction with EtMgBr

Figure 91. The diastereomeric products of a Grignard addition reaction to **165**.

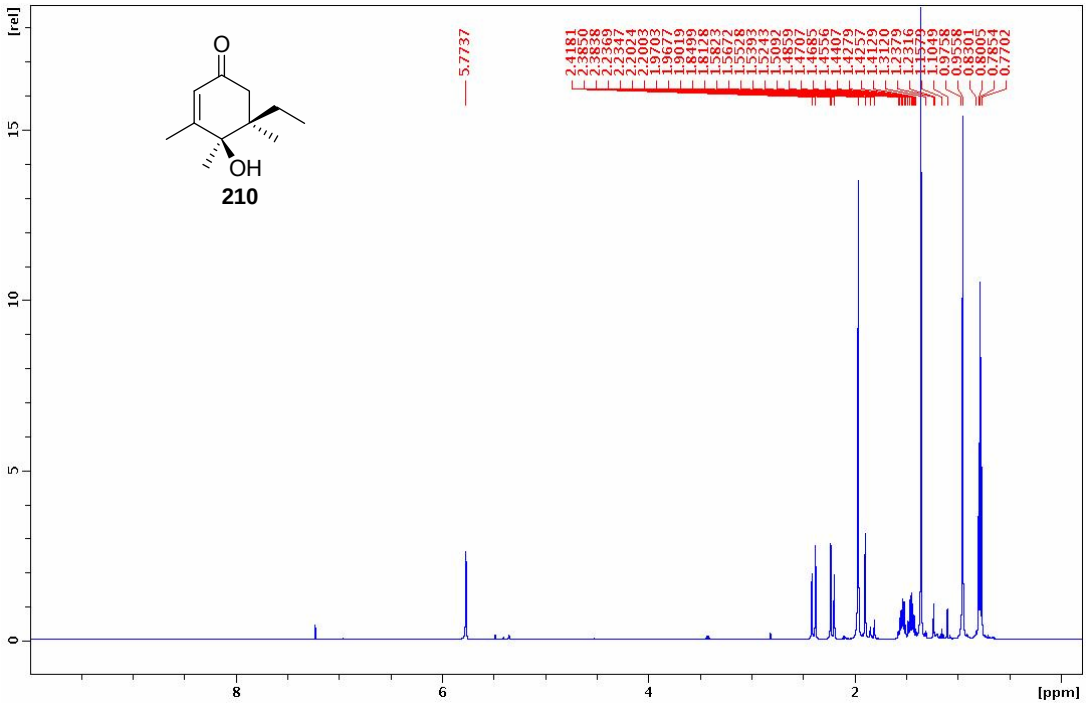


Figure 92. ^{1}H NMR spectrum of compound **210**.

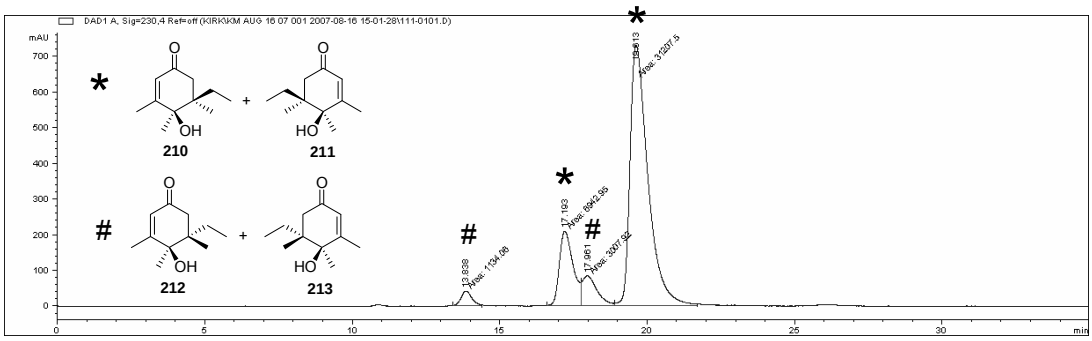
2.1.4.2 Separation of the Trialkylaluminum Reaction Mixture.

The reaction product mixture **210, 211, 212 and 213** in Figure 90 produced an HPLC chromatogram that displayed 4 peaks at 230 nm (Figure 51). The four compounds were separated and collected by preparative HPLC (Figure 93). The compounds from the peaks at 13.8 min and 17.9 min produced identical ^{1}H NMR spectra (Figure 94) and were found to be enantiomers. The compounds from the peaks at 17.2 min and 19.6 min produced identical ^{1}H NMR spectra (Figure 94) and were also found to be enantiomers. The peaks of the HPLC chromatogram from the organoaluminum reaction where then compared to the peaks of the HPLC chromatogram from the Grignard reaction. The compounds represented by the HPLC peaks at 17.2 min and 19.6 min were found to be either compound **210** or **211**. The optical rotations confirmed that the compounds represented by the HPLC peaks at 13.8 min and 17.9 min were enantiomers (Table 17, Entries 1 and 3). In addition, the optical rotations confirmed that the compounds represented by the HPLC peaks at 17.2 min and 19.6 min were enantiomers.

Table 17. Optical rotations of compounds **210**, **211**, **212** and **213**.

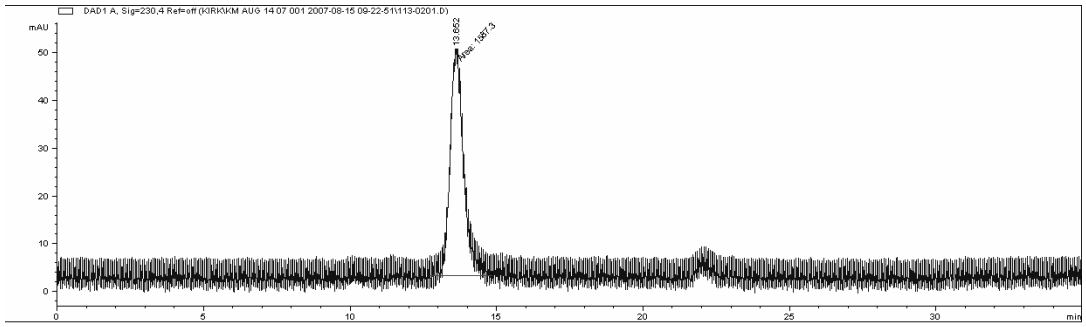
Entry	HPLC Chromatograms Peak (min)	$[\alpha]_{365}^{20}$
1	13.8	-29
2	17.2	-57
3	17.9	+29
4	19.6	+57

Isolation of diastereomeric compounds by HPLC:



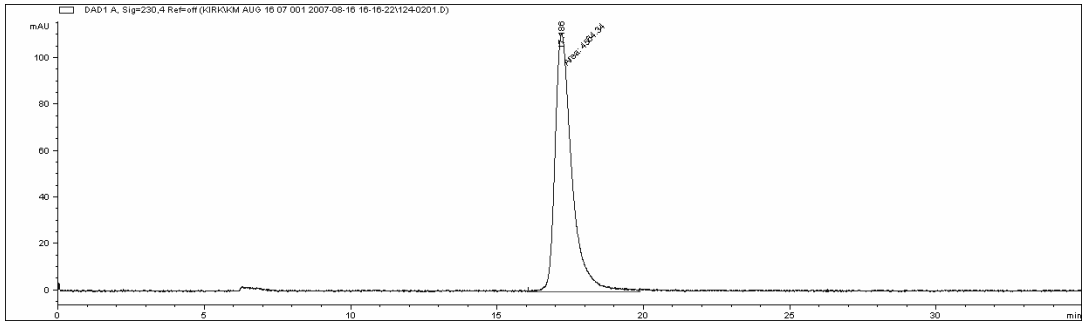
--Peak retention times: 13.8, 17.2, 17.9 and 19.6.

HPLC of 1st peak:



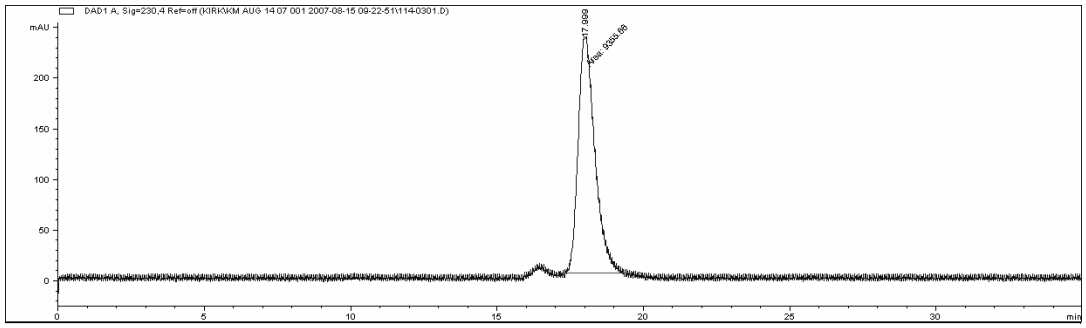
--Peak retention time: 13.8; $[\alpha]_{365}^{20}$ -29 (c 0.1, $CHCl_3$)

HPLC of 2nd peak:



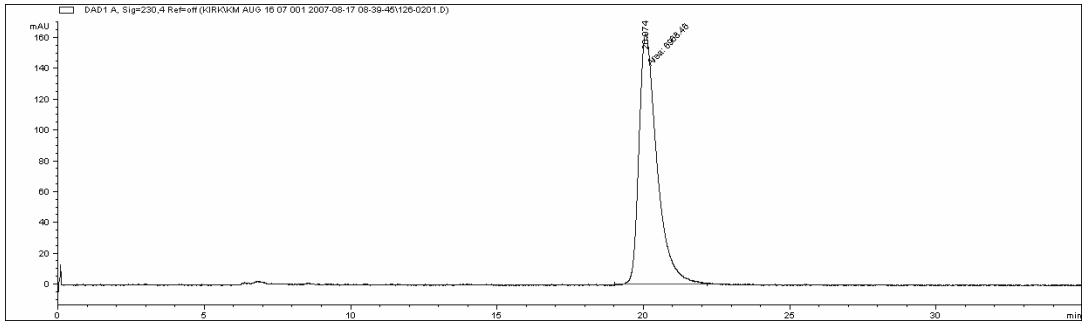
--Peak retention time: 17.2; $[\alpha]_{365}^{20}$ -57 (c 0.1, $CHCl_3$)

HPLC of 3rd peak:



--Peak retention time: 17.9; $[\alpha]_{365}^{20}$ +29 (c 0.1, $CHCl_3$)

HPLC of 4th peak:



--Peak retention time: 19.6; $[\alpha]_{365}^{20}$ +57 (c 0.1, $CHCl_3$)

Figure 93. HPLC chromatograms of the isolated compounds **210**, **211**, **212** and **213**.

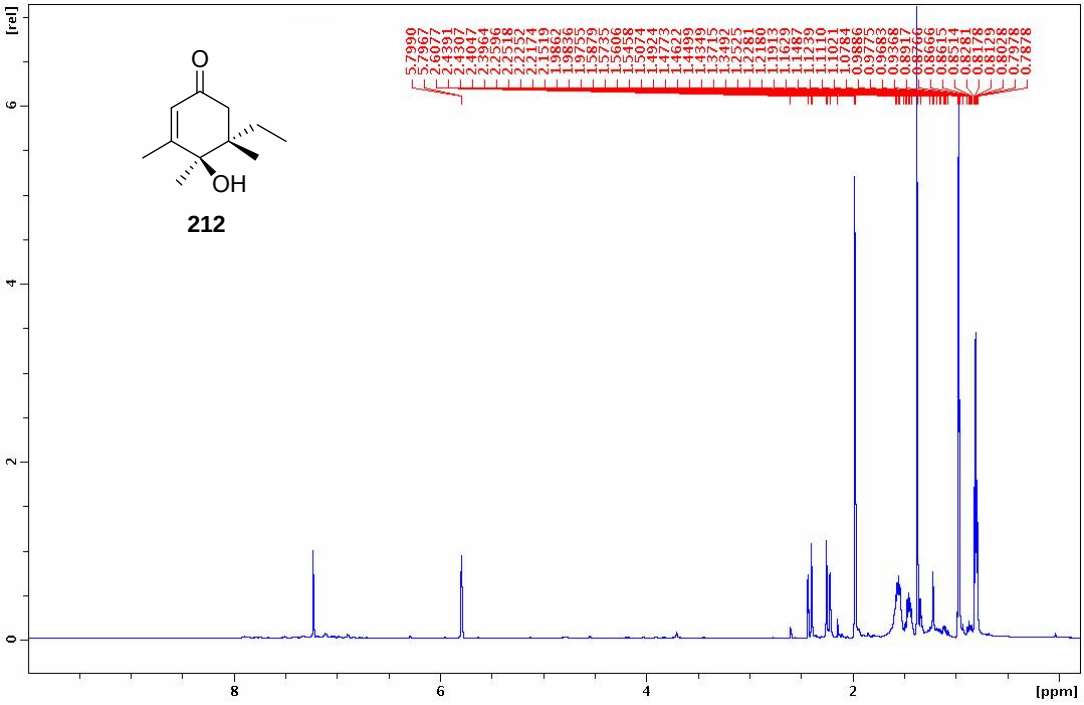


Figure 94. ^{1}H NMR spectrum of compound **212**.

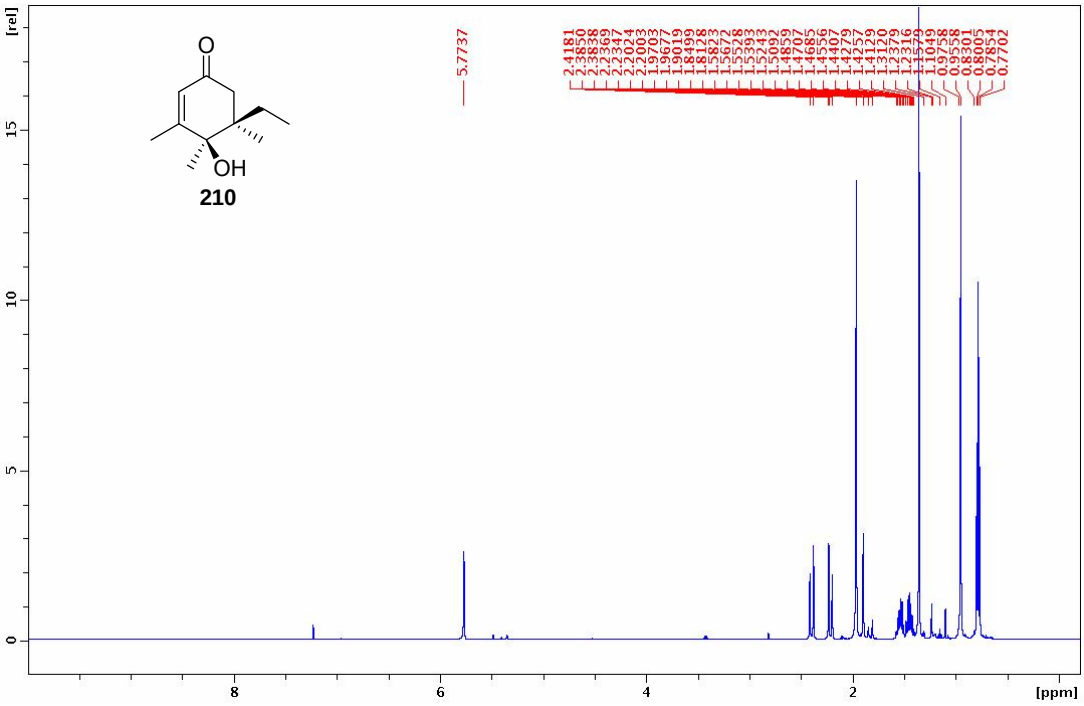


Figure 95. ^{1}H NMR spectrum of compound **210**.

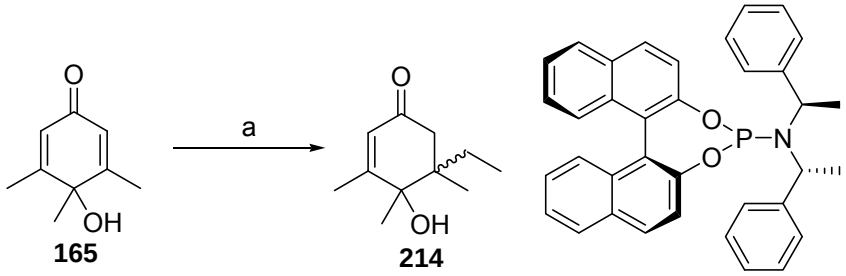
Table 18. Chemical shifts of the 1H NMR spectrum for the diastereomers **210** and **212**.

Compounds 210 and 211			
Entry	**Proton**	**Chemical Shift (ppm)**	**Multiplicity (Hz)**
1	HC-2	5.77	1H, s
2	HC-6	2.38	1H, d, J = 17.9
3	HC-6	2.23	1H, d, J = 17.9
4	H_3C-7	1.97	3H, s
5	H_2C-10	1.54	2H, m
6	H_2C-10	1.46	2H, m
7	H_3C-8	1.36	3H, s
8	H_3C-9	0.96	3H, s
9	H_3C-11	0.77	3H, t, J = 7.6
Compounds 212 and 213			
Entry	**Proton**	**Chemical Shift (ppm)**	**Multiplicity (Hz)**
10	HC-2	5.80	1H, s
11	HC-6	2.39	1H, d, J = 17.9
12	HC-6	2.23	1H, d, J = 17.9
13	H_3C-7	1.98	3H, s
14	H_2C-10	1.55	2H, m
15	H_2C-10	1.47	2H, m
16	H_3C-8	1.37	3H, s
17	H_3C-9	0.94	3H, s
18	H_3C-11	0.79	3H, t, J = 7.6

The diastereomers **210** and **212** were structurally characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and UV. The ^{1}H NMR spectra of the two diastereomers **210** and **212** each displayed 9 expected peaks at similar chemical shifts (Figure 94 and 95). The syn addition diastereomer **210** possessed a singlet peak at 5.77 ppm and two doublet peaks at 2.38 ppm and 2.23 ppm. The peaks represented the olefinic (HC-2, HC-6) protons respectively (Table 18, Entries 1, 2 and 3). The vinyl methyl (H_3C-7), and the two remaining methyl (H_3C-8, H_3C-9) protons were found to be represented by singlet peaks at 1.97 ppm, 1.36 ppm and 0.96 ppm, respectively (Table 18, Entries 4, 7 and 8). The final ethyl group protons (H_2C-10, H_3C-11) were represented by two double quartet peaks at 1.54 ppm and 1.46 ppm as well as a triplet peak at 0.77 ppm (Table 18, Entries 5, 6 and 9). The anti addition diastereomer **212** possessed almost all identical chemical shifts with the exception of the triplet peak representing a section of the ethyl group (H_3C-11) which was

found at 0.79 ppm (Table 18, Entry 18). The ^{13}C NMR spectrum of each diastereomer further supported their structures by revealing 11 peaks representing the correct number of magnetically nonequivalent carbons. The IR spectra of each diastereomer revealed the presence of a hydroxyl stretch at 3427 cm^{-1} and a carbonyl stretch at 1648 cm^{-1}. Further proof was attained from the electron impact mass spectra of each diastereomer where the molecular ion peaks were both found to be 182.1304 (calc. 182.1307). In addition, the mass spectra of each diastereomer also displayed a base peak at 112 m/z which indicated that a retro Diels-Alder fragmentation reaction was occurring in the mass spectrometer. Lastly, the UV spectrum of the two diastereomers depicted a single absorption at 238 nm with an extinction coefficient of 1.5 x 10^4 $M^{-1}\cdot cm^{-1}$ which is in agreement with known literature values of a α,β-unsaturated ketone chromophores.[131]

2.1.4.3 Expansion of the Trialkylaluminum ECA.



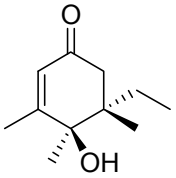
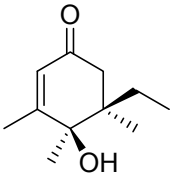
a) Et_3Al, CuTC, (**26**), Et_2O, -15°C.

Figure 96. Altering the conditions of an ECA reaction with trialkylaluminum reagents.

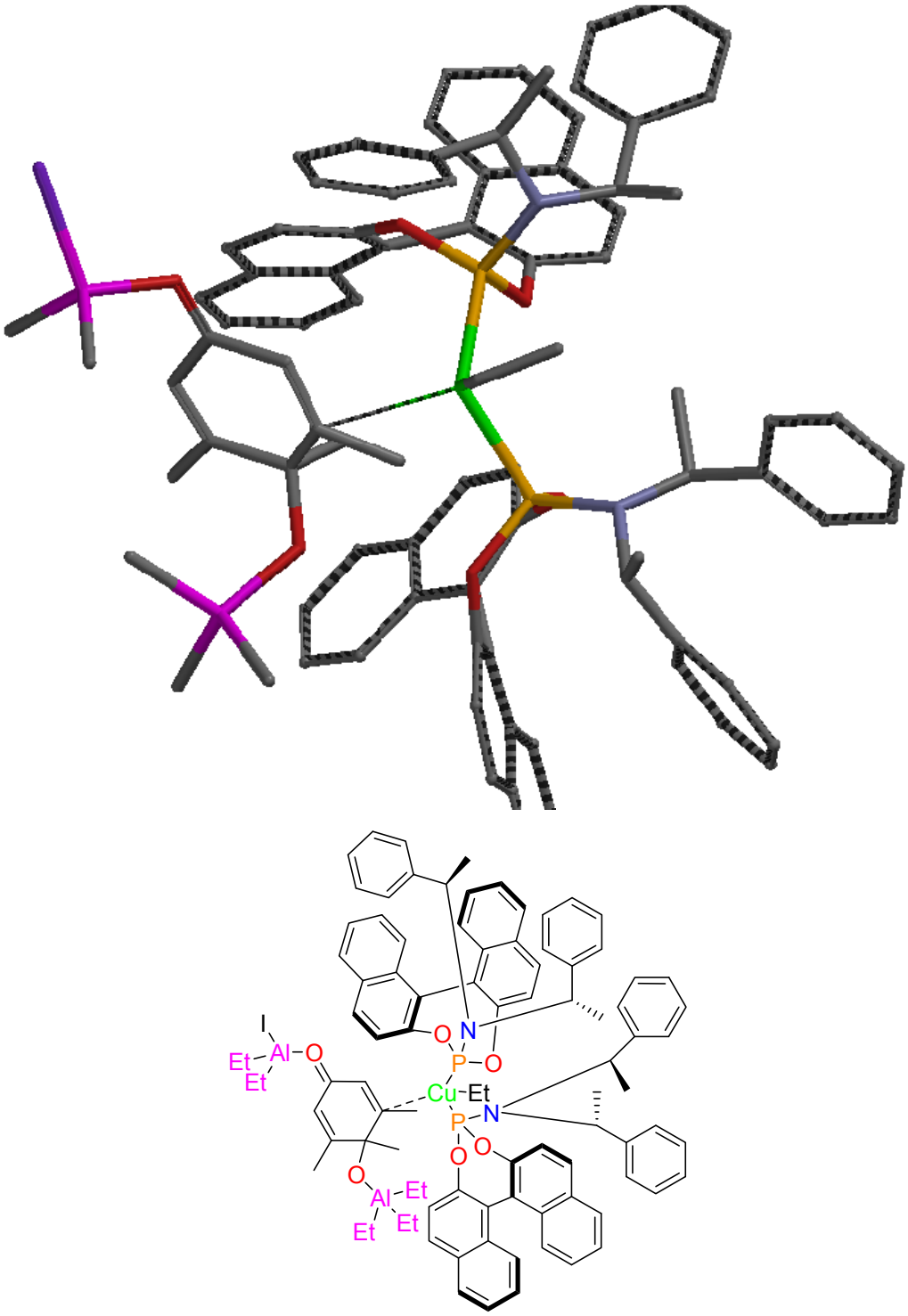
In an effort to increase the yield of the reaction a series of different variables were altered (Figure 96). The time of the reaction was increased from 18 hours to 72 hours (Table 19, Entry 1) but, unfortunately there was no increase in yield. The results from entry 1 indicated that the catalyst was being poisoned. Therefore, in an attempt to counter this poisoning effect the equivalents of chiral ligand were

doubled. Unfortunately, the doubling of chiral ligand equivalents resulted in a slight drop in yield (Table 19, Entry 2). The addition of a Lewis acid has been reported to increase chemical yields during alkylaluminum conjugate additions.[148] The addition of the Lewis acid $AlBr_3$ to this study (Table 19, entry 3) was found to be detrimental and no reaction occurred. In a final effort to increase the yield of the reaction the temperature of the reaction was elevated to 0°C and room temperature (Table 19, entries 4 and 5). The elevation in temperature produced a mixture of products. The mixture included the desired product compounds **210**, **211**, **212** and **213** and some other unidentified rearrangement product. Due to the similarity in polarities of the products within the mixture, there was a great difficulty in obtaining the pure products **210**, **211**, **212** and **213**. A different alkylating reagent Me_3Al was attempted (Table 19, entry 7), but again no reaction was observed. The reaction was also attempted with a methyl ether substrate **197** and the precursor to synthesize MeABA **161** (Table 19, Entries 6 and 8), but no reaction was observed. This result shows that the γ-substituent affected the reaction. A transition state model was constructed based on the catalytic mechanism of ECA reactions using alkylaluminum reagents[87] in an attempt to explain this result (Figure 97). The model suggested that there was a possible steric interaction between γ-substituents and the binaphtol group from the ligand **26**. Another interesting observation was that unlike previous experiment the β-substituent seemed to fit comfortably without a steric interaction.

Table 19. ECA with trialkylaluminum using altered conditions.

Entry	Ligand	T (°C)	t (h)	dr[a]				Yield (%)
				 -anti addition to OH		 -syn addition to OH		
				(-)	(+)	(-)	(+)	
1	**26**	-15	72	30	12	8	50	13
2	(2 equiv) **26**	-15	18	60	5	11	24	11
3	($AlBr_3$) **26**	-15	18	--	--	--	--	NR
4	**26**	0	18	7	14	14	65	27[b]
5	**26**	23	18	8	17	10	65	35[b]
6[c]	**26**	-15	18	--	--	--	--	NR
7[d]	**26**	-15	18	--	--	--	--	NR
8[e]	**26**	-15	18	--	--	--	--	NR

[a]dr determined by chiral HPLC analysis ((R,R)-Whelk-01). [b]Product was obtained as a mixture of the desired product and a rearrangement byproduct. [C]**197** was used as a starting material. [d]Me_3Al was used as the alkylating reagent. [e]**157** was used as a starting material.

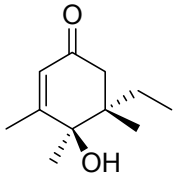
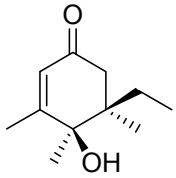


215

Figure 97. Transition state model of an ECA reaction using triethylaluminum and compound **165**.

Trialkylaluminum reagents are known to react with functionalities such as ketones and alcohols to produce rearrangement products[149]. The number of equivalents of alkylaluminum reagent was thought to possibly influence the yield of the desired product **165**. Therefore, the effects of different equivalents of alkylaluminum reagent were examined in as reported in Table 19. Table 20, entry 1, the same number of equivalents as Alexakis' result, produced the highest yield with modest enantioselectivity. The doubling of Et_3Al equivalents (Table 20, entry 2) resulted in a slight drop in yield but, the enantioselectivity of anti diastereomer was reversed from 7:17 to 27:16. Decreasing the equivalents of Et_3Al (Table 20, entries 3 and 4) resulted in modest enantioselectivities but lower yields. Overall the major stereoisomer in all cases was the (+)-syn addition product.

Table 20. ECA to **165** using Alexakis' reaction conditions and different equivalents of Et_3Al.

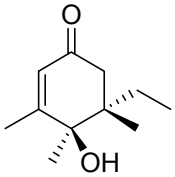
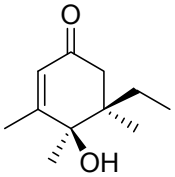
Entry	**Equivalent Et_3Al**	**dr[a]**				**Yield (%)**
		 **-anti addition to OH**		 **-syn addition to OH**		
		(-)	**(+)**	**(-)**	**(+)**	
1	1.4	7	17	16	60	15
2	2.8	27	16	7	49	11
3	0.7	9	11	17	63	10
4	0.4	33	8	19	40	3

[a]dr determined by chiral HPLC analysis ((R,R)-Whelk-01).

Solvent can have a major role in the formation of carbaions and their subsequent reaction with electrophiles. The choice of solvent will influence the aggregation states of the alkylating reagents. The effect of some commonly used solvents, for the reaction of compound **165** with triethylaluminum and the phosphoramidite ligand **26** were surveyed in Table 21. The reaction using Et_2O gave the best yield (Table 21, entry 1). The reaction using PhMe gave a lower yield than Et_2O but displayed a slightly better selectivity where one diastereomer, the

addition product syn to the hydroxyl moiety, was enantiomerically pure with the (+)-form predominating (Table 21, entry 2). The reaction using THF gave the lowest yield but demonstrated good selectivity where again one diastereomer, the addition product anti to the hydroxyl moiety, was enantiomerically pure with the (-)-form predominating (Table 21, entry 3). As a result, the ECA reaction between triethylaluminum and compound **165** achieved higher yields in non-coordinating solvents then in coordinating ones. Alexakis also observed this trend when performing conjugate additions to cyclic enones with dialkylzinc reagents.[36,54] In addition, the (+)-syn addition was the major stereoisomer in non-coordinating solvents. In THF, a coordinating solvent, the major stereoisomers were both the (+)-syn addition and the (-)-anti addition products.

Table 21. ECA to **165** using Alexakis' reaction conditions in different solvents.

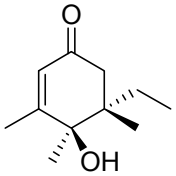
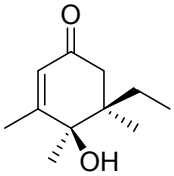
Entry	**Solvent**	**dr[a]**				**Yield (%)**
		 **-anti addition to OH**		 **-syn addition to OH**		
		(-)	**(+)**	**(-)**	**(+)**	
1	Et_2O	7	17	16	60	15
2	PhMe	12	18	<1	70	11
3	THF	41	<1	19	40	7

[a]dr determined by chiral HPLC analysis ((R,R)-Whelk-01).

Copper-catalyzed conjugate addition reactions to enones are highly sensitive to the nature of the copper salt used.[150] The effects of some commonly used Cu salts in conjugate addition chemistry were surveyed in Table 22. Alexakis' system made use of CuTC which produced the highest yield and modest enantioselectivities (Table 22, entry 1). The copper halide salts CuCl, CuI and $CuBr{\cdot}SMe_2$ also produced modest enantioselectivities but poor yields (Table 22, entries 2, 3 and 6). The remaining triflate salts produced similar yields and enantioselectivities to that of the CuTC reaction (Table 22, entries 4 and 5). Overall the (+)-syn addition

product was the major stereoisomer. However, with the exception of the CuTC and $Cu(OTf)_2$ entries, the syn addition products were produced with poor enantioselectivity. For example, the reactions using CuCl and $CuBr{\cdot}SMe_2$ produced mostly syn addition racemic products.

Table 22. ECA to **165** using Alexakis' reaction conditions with different Cu salts.

Entry	**Cu Salt**	**dr[a]**				**Yield (%)**
		 **-anti addition to OH**		 **-syn addition to OH**		
		(-)	**(+)**	**(-)**	**(+)**	
1	CuTC	7	17	16	60	15
2	CuCl	3	7	40	50	5
3	CuI	3	7	38	52	3
4	Cu(OTf)	10	9	32	49	11
5	$Cu(OTf)_2$	17	7	16	60	13
6	$CuBr{\cdot}SMe_2$	<1	5	46	49	2

[a]dr determined by chiral HPLC analysis ((R,R)-Whelk-01).

The success of the phosphoramidite ligand resulted in a further study of that family of ligands. As a result, the ligands (Figure 98) were screened using the same conditions as in Figure 89.

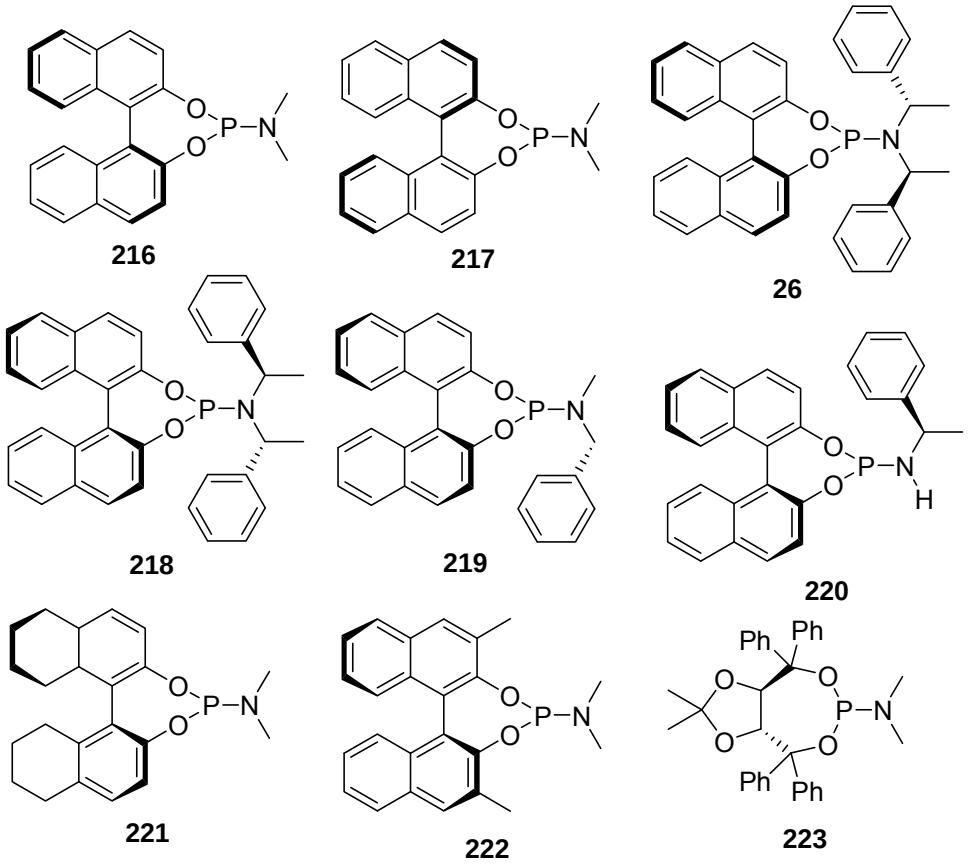
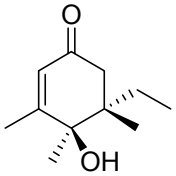
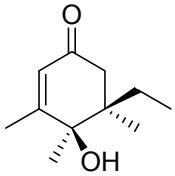


Figure 98. Phosphoramidite ligands screened.

Table 23. ECA to **165** using Alexakis' reaction conditions with different ligands.

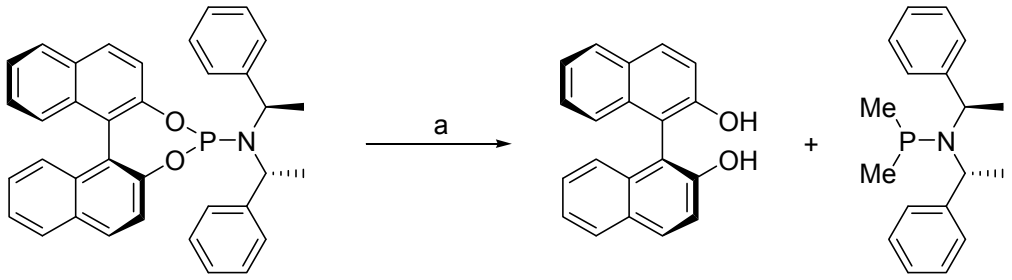
Entry	Ligand	dr[a]				Yield (%)
		 **-anti addition to OH**		 **-syn addition to OH**		
		(-)	**(+)**	**(-)**	**(+)**	
1	**216**	21	23	<1	56	6
2	**217**	50	15	<1	35	6
3	**26**	7	17	16	60	15
4	**218**	46	2	<1	52	12
5	**219**	64	16	<1	20	4
6	**220**	37	29	<1	34	3
7	**221**	70	10	<1	20	5
8	**222**	80	<1	<1	20	3
9	**223**	70	15	<1	15	2

[a]dr determined by chiral HPLC analysis ((R,R)-Whelk-01).

The binaphthol chiral ligands **26** and **218** produced the best yields. However, the two ligands produced very different selectivities. Ligand **218** produced two diastereomers that were almost enantiomerically pure, whereas, ligand **26** produced two diastereomers; both that possessed modest enantioselectivity. Even though the ligands **26** and **218** are very similar in structure with the exception of the amine configurations the results show a matched/mismatched effect. This matched/mismatched was also observed by Alexakis[18] where similar binaphthol ligands were used. The remaining phosphoramidite ligands tested produced modest enantioselectivities where one diastereomer was enantiomerically pure but, much poorer yields were also achieved. One structural difference between the remaining ligands and ligands **26** and **218** is the amine functionality. The reaction was observed to function with highest yields when the amine functionality possessed two large chiral bulky substituents. Ligands **219** and **220** demonstrated that one large chiral substituent on the amine functionality resulted in poor yields. Ligands **221**, **222** and **223** all possessed an altered binaphthol backbone structure. As a result, these reactions favoured the (-)-anti addition product. Based on the model

above (Figure 98) an altered binaphthol backbone structure must reorientate compound **165** so that the addition occurs on the opposite face of the one containing the OH group.

Recently, several examples of the use of trialkylaluminum reagents as nucleophiles in copper-catalyzed asymmetric transformations with phosphoramidite ligands have been described[151]. In addition, the sense of chirality of the amine part of the ligand has proven to exert a major influence on the stereochemical outcome of the reaction (Table 23, entries 3 and 4), with an almost complete reversal of absolute configuration. These results conflict with the normal trend in which the BINOL part controls the enantioselectivity in conjugate additions.[151] In 2006, Alexakis, while working on asymmetric transformations using bicyclic hydrazines,[152] observed by phosphorus NMR a reaction between the phosphoramidite ligands and alkylaluminum reagents. Alexakis observed a complete disappearance of the characteristic phosphorous signal of the phosphoramidite ligand **26** as soon as a solution of Me_3Al was added to the same NMR tube. After further workup and chromatographic purification, Alexakis isolated two compounds **224** and **225** (Figure 99).



26 **224** **225**

a) Me_3Al, CH_2Cl_2.

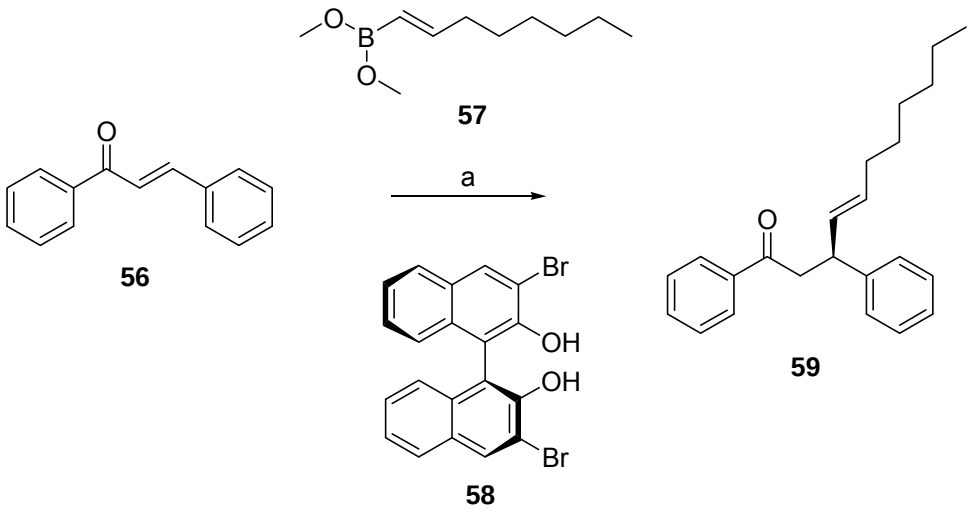
Figure 99. Degradation of phosphoramidite ligand **26** in the presence of Me_3Al.

Alexakis concluded that **225** formed in situ based on the cleavage of the BINOL moiety by an organoaluminum reagent triggered by a precoordination.[153] The degradation of the phosphoramidite ligand was also found to be much slower in

more coordinating solvents such as THF or with the less-oxophilic organozinc reagents. In Alexakis' system ligand **225** appeared to be the real ligands in the copper-catalyzed nucleophilic ring opening of bicyclic hydrazines. This study indicates that perhaps the catalyst is being degraded by the alkylating reagent in combination with the selected solvent and thus accounting for the poor yields.

2.1.5 Boronic Acid Conjugate Additions.

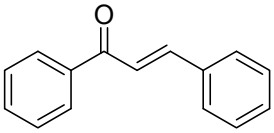
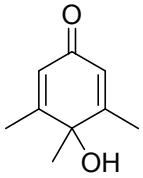
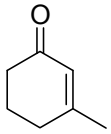
Boronic acids have been used to perform conjugate addition reactions.[77,91] Chong demonstrated a 1,4-alkenylation of chalcone **56** using a boronate **57** and catalytic amounts of binaphthol **58** (Figure 100).[77] The reported reaction conditions by Chong were repeated and validated. Chong's reaction conditions were successfully repeated (Table 24, Entry 1). A yield of 88% was comparable to Chong's yield of 92%. However, the enantioselectivity of 90%was 8% lower than the enantioselectivity reported by Chong.



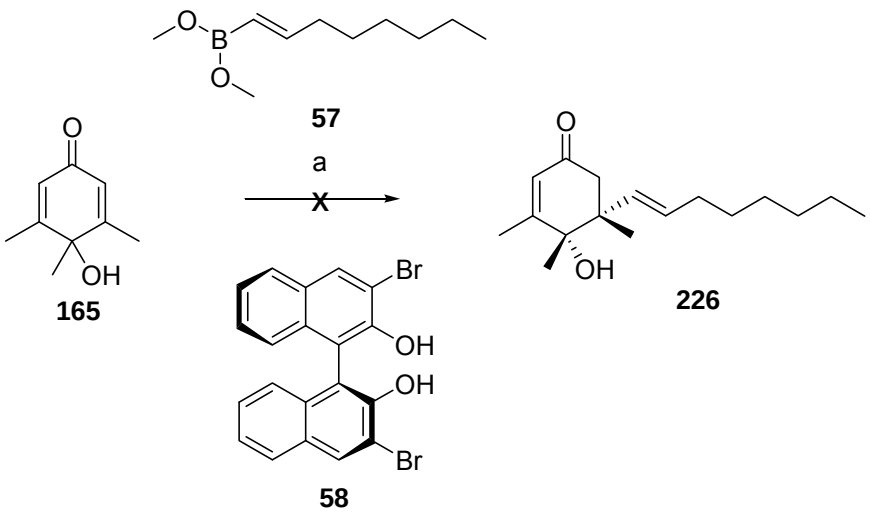
a) (**57**), (**58**), CH_2Cl_2, 4A MS, 40°C.

Figure 100. Chong's ECAs reported conditions using boronic acids.

Table 24. Reactions using boronic esters reported by Chong.

Entry	Enone	Yield (%)	ee[a]
1	 **56**	88	90
2	 **165**	NR	--
3	 **24**	NR	--

[a]ee determined by chiral HPLC analysis (Chiralcel-OD).



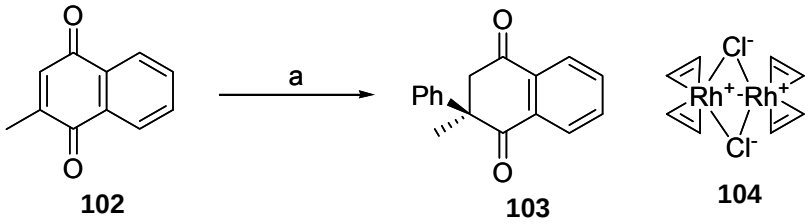
a) (**57**), (**58**), CH_2Cl_2, 4A MS, 40°C.

Figure 101. Boronic ester reaction to **165** using conditions reported by Chong.

After validating the boronic ester reaction conditions published by Chong, the method was applied to **165** (Figure 101). Unfortunately no reaction was observed between compound **165** and the boronic ester using the chiral diol **58** (Table 24, Entry 2). As a result, the reaction was attempted with a simple substrate

3-methyl-2-cyclohexen-1-one **24** in order to determine whether the β-methyl substituent was hindering the reaction. No reaction was observed with substrates **24**. The β-methyl substituent was sterically hindering the reaction.

Conjugate addition of boronic acids to β-substituted enones has been reported by Hayashi.[91] Hayashi reported a rhodium-catalyzed ECA of arylboronic acid to 2-methyl-1,4-naphthoquinone providing a 1,4 addition product (Figure 102). Thus, the reported reaction conditions by Hayashi, summarized in Table 25, were validated. Hayashi's reaction conditions were successfully repeated (Table 25, Entry 1). A yield and enantioselectivity of 70% and 99% respectively were identical to Hayashi's report.

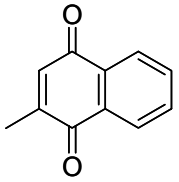
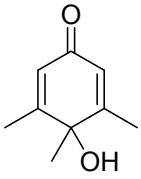
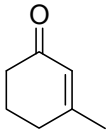
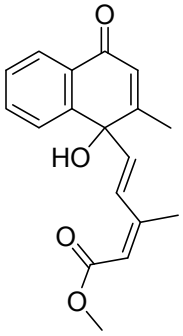
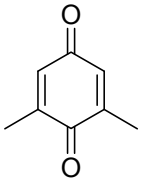


102 **103** **104**

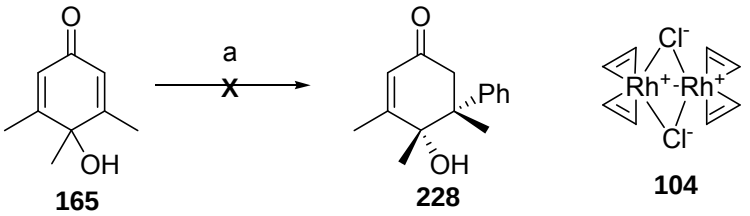
a) $PhB(OH)_2$, (R)-binap, (**104**), KOH, Dioxane/H_2O, 50°C.

Figure 102. Hayashi's ECAs reported conditions using boronic acids.

Table 25. Reactions using boronic acids reported by Hayashi.

Entry	Enone	Yield (%)	ee[a]
1	 **102**	70	99
2	 **165**	NR	--
3	 **24**	NR	--
4	 **227**	NR	--
5	 **175**	NR	--

[a]ee determined by optical rotation from literature value, $[\alpha]_D^{20} = +29.0$ (c 0.1, $CHCl_3$).



a) $PhB(OH)_2$, (R)-binap, (**104**), KOH, Dioxane/H_2O, 50°C.

Figure 103. Boronic acid reaction using conditions reported by Hayashi to **165**.

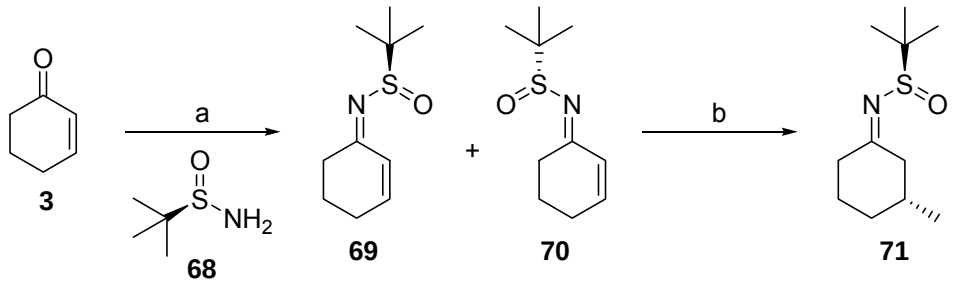
After validating the reaction conditions (Table 25, Entry 1) published by Hayashi, the method was applied to **165** (Figure 103). Unfortunately no reaction was observed between compound **165** and arylboronic acid (Table 25, Entry 2). Hayashi reported a possible transition state where compound **102** fits into a pocket formed by the rhodium-phosphine catalyst. As a result, in order to test this hypothesized transition state, a variety of substrates were attempted with this reaction. Firstly, the reaction was attempted with 3-methyl-2-cyclohexen-1-one **24** in order to determine whether the reaction was not proceeding due to the γ-substituents. The γ-substituents of **165** possessed sp^3 bonds versus the γ-substituent of the model that was an sp^2 bonded carbonyl moiety. Nonetheless, compound **24** did not react. Compound **227** was then used as a substrate for this reaction to observe whether the naphthoquinone backbone structure was necessary for the reaction to proceed. However, there was no reaction between arylboronic acid and compound **227**. In a final effort to understand this system, compound **175** was used as a starting substrate in this reaction. It was hypothesized that the two sp^2 bonded carbonyls acted as coordinating structures. This was not the case, as again no reaction occurred. As a result, it was shown that both the ketone and aromatic regions of compound **102** are required for this reaction to proceed.

2.2 Diastereoselective Conjugate Addition (ECA) Methods Using a Chiral Auxiliary

Although this study was aimed at developing a stereoselective addition to compound **165** via an ECA, the lack of reactivity and low yields attained from enantioselective methods forced this project in a different direction. A decision was made to begin focusing efforts with a diastereoselective method using a chiral auxiliary. However, if this newly developed system was to be applied to the ABA total synthesis the chiral auxiliary could be bonded at specific locations on compound **165**. Firstly, a chiral auxiliary was used to react with compound **165** to form a chiral intermediate.

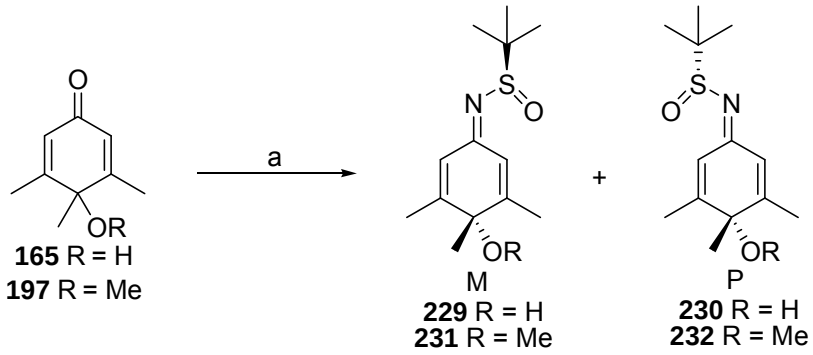
2.2.1 Synthesis of tert-Butanesulfinyl Imines

Sulfinamides have been used as chiral auxiliaries in combination with similar enones to compound **165** to form reactive sulfinyl imines intermediates. These sulfinyl imine intermediates have been used to perform diastereoselective conjugate additions.[82] Ellman demonstrated the use of a sulfonamide **68** and 2-cyclohexen-1-one **3** to produce N-tert-butanesulfinyl imines **69** and **70**. The N-tert-butanesulfinyl imine products were then submitted to a diastereoselective conjugate addition reaction to provide the enantioenriched amine product **71** (Figure 104).[82] The reported reaction conditions by Ellman were then validated. Ellman's reaction conditions were successfully repeated (Table 26, Entry 1). A yield and diastereomeric ratio of 86% and 2:1 was obtained identical to Ellman's results.



a) $Ti(OEt)_4$, (**68**), THF, Reflux. b) CuX, MeLi, Et_2O, -78°C.

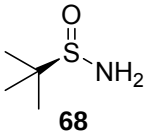
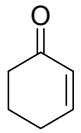
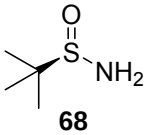
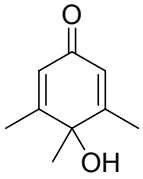
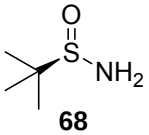
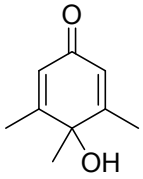
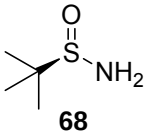
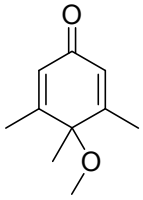
Figure 104. Ellman's ECA via the formation of a sulfinyl imine intermediate.



a) (**68**), $Ti(OEt)_4$, 4A MS, PhMe, Reflux.

Figure 105. Sulfinyl imine formation from compounds **165** and **197**.

Table 26. Sulfinyl imine formation.

Entry	Chiral Auxiliary	Enone	Solvent	t (h)	Yield (%)	dr[a]
1	 **68**	 **3**	THF	24	86	66:33
2	 **68**	 **165**	THF	24	NR	--
3	 **68**	 **165**	PhMe	24	40	55:45
4	 **68**	 **197**	PhMe	24	70	55:45

[a]dr ratio was measured by comparing the integration of peaks 6 and 6' of the ^{1}H NMR (Figure 106).

After validating reaction conditions published by Ellman, the conditions were applied to compound **165** (Figure 105). Unfortunately no reaction was observed (Table 26, Entry 2) between compound **165** and the sulfonamide **68** in THF. The solvent was then changed to PhMe and the temperature was increased. As a result, the reaction was successful in producing compounds **229** and **230** with 40% yield. In addition, the ^{1}H NMR of the mixture of compounds **229** and **230** displayed a 1.2:1 diastereomeric ratio (Figure 106).

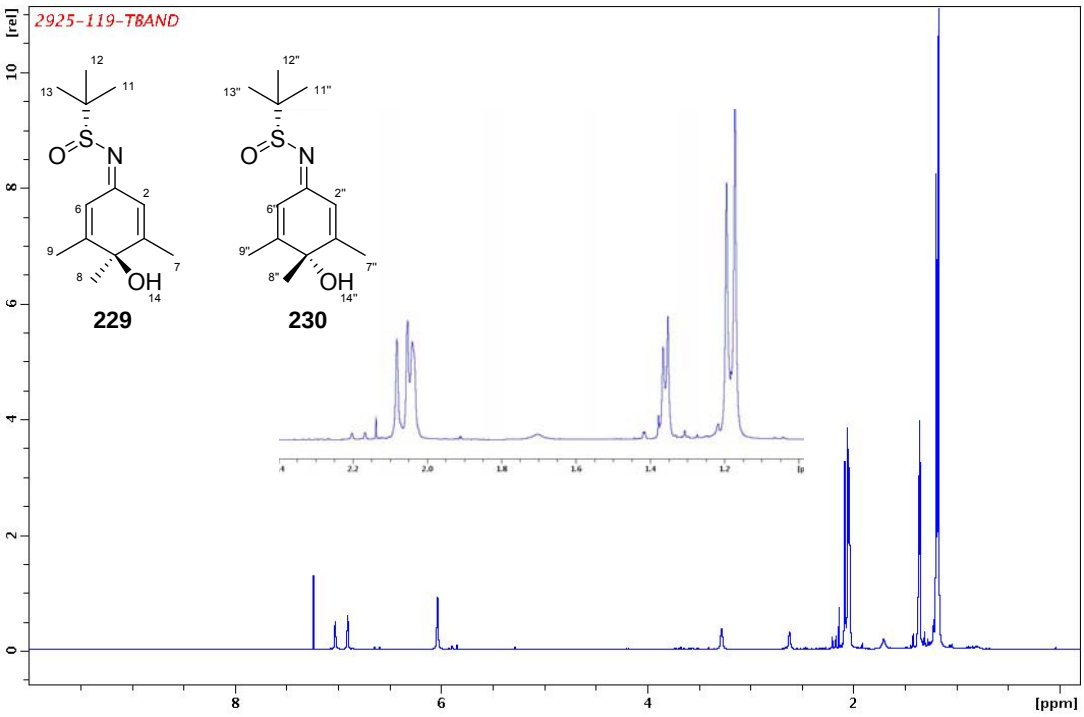


Figure 106. ^{1}H NMR spectrum of the sulfinyl imine intermediates **229** and **230**.

Table 27. Chemical shifts of the ^{1}H NMR spectrum of compounds **229** and **230**.

Entry	Proton	Chemical Shift (ppm)	Multiplicity (Hz)
1	HC-6''	7.01	1H, s
2	HC-6	6.93	1H, s
3	HC-2, HC-2''	6.04	2H, s
4	HO-14''	3.31	1H, s
5	HO-14	2.80	1H, s
6	H_3C-7, H_3C-9, H_3C-7'', H_3C-9''	2.07-2.03	12H, s
7	H_3C-8	1.36	3H, s
8	H_3C-8''	1.35	3H, s
9	H_3C-11, H_3C-12, H_3C-13	1.21	9H, s
10	H_3C-11'', H_3C-12'', H_3C-13''	1.19	9H, s

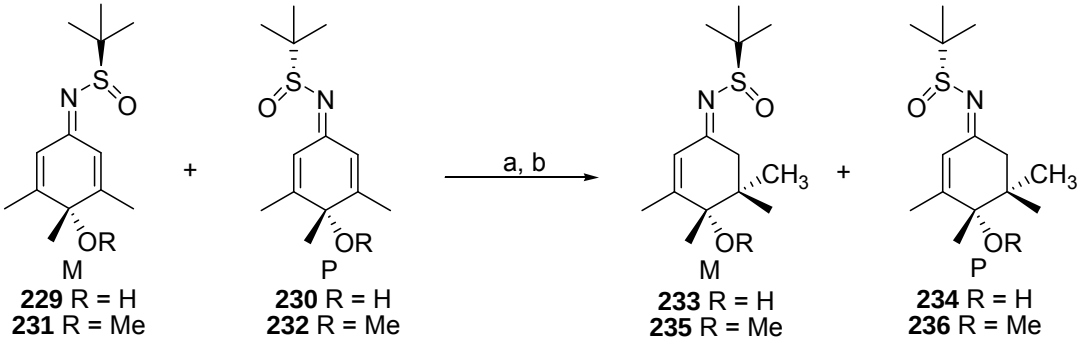
The mixture of diastereomers **229** and **230** could not be separated by HPLC. Thus, the mixture was characterized ^{1}H NMR, ^{13}C NMR, IR, MS and UV. The ^{1}H NMR spectrum (Figure 106) displayed 10 expected peaks at 7.01 ppm, 6.93 ppm, 6.04 ppm, 3.31 ppm, 2.80 ppm, 2.07 ppm, 1.36 ppm, 1.35 ppm, 1.21 ppm and 1.19 ppm. The singlet peaks in the aromatic region at 7.01 ppm and 6.93 ppm

represented the two olefinic (HC-6, HC-6'') protons interacting with the sulfoxide moiety (Table 27, Entries 1 and 2). The opposing unaffected free olefinic (HC-2, HC-2'') protons were found to be represented by a singlet peak at 6.04 ppm (Table 27, Entry 3). The vinyl methyl protons (H_3C-7, H_3C-9, H_3C-7'', H_3C-9'') were found to be represented by a multiplet made up of four singlet peaks at 2.03-2.07 ppm (Table 27, Entry 6). The remaining methyl protons (H_3C-8, H_3C-8'') were found to be represented by two singlet peaks at 1.36 ppm and 1.35 ppm, respectively (Table 27, Entries 7 and 8). The hydroxyl group (HO-14'', HO-14) protons were represented by two broad singlet peaks at 3.31 ppm and 2.80 ppm (Table 27, Entries 4 and 5). Finally, the tert-butyl group protons (H_3C-11, H_3C-12, H_3C-13, H_3C-11'', H_3C-12'', H_3C-13'') were found to be represented by two large singlet peaks at 1.21 ppm and 1.19 ppm (Table 27, Entries 9 and 10). The ^{13}C NMR spectrum supported the structures of the diastereomers **229** and **230** by revealing 22 peaks representing the correct number of magnetically nonequivalent carbons. For example, the ^{13}C NMR spectrum demonstrated 12 peaks at 165.40 ppm (C-1'''), 164.25 ppm (C-1'), 159.65 ppm (C-3'''), 158.61 ppm (C-3'), 157.14 ppm (C-5'''), 155.80 ppm (C-5'), 125.50 ppm (C-6'''), 125.19 ppm (C-6'), 118.11 ppm (C-2'''), 117.61 ppm (C-2'), 71.26 ppm (C-4''') and 71.12 ppm (C-4') representing the two 6 carbon ring structures of the two diastereomers. The ^{13}C NMR spectrum also showed 5 peaks at 57.60 ppm (C-10'''), 57.07 ppm (C-10'), 22.90 ppm (C-13''',C-13'), 22.48 ppm (C-12''', C-12') and 22.26 ppm (C-11''', C-11') representing the two tert-butyl group sets of carbon atoms. The remaining 5 peaks in the spectrum at 25.76 ppm (C-8'''), 25.54 ppm (C-8'), 18.81 ppm (C-7''',C-7'), 18.07 ppm (C-9''') and 17.93 ppm (C-9') represented the 6 methyl group carbon atoms. The IR spectrum revealed the presence of a hydroxyl stretch at 3283 cm^{-1}, an imine absorption at 1543 cm^{-1} and a sulfoxide absorption at 1043 cm^{-1}. Further proof was attained from the electron impact mass spectrum where a molecular ion peak of 256.1378 was found. Lastly, the UV spectrum of the diastereomers **229** and **230** portrayed a single absorption at 254 nm an extinction coefficient of 2.3 x 10^4 $M^{-1}\cdot cm^{-1}$ which is in agreement with the literature value of similar sulfinyl imines with extended conjugation.[131]

Methyl ether compound **197** also reacted with the sulfonamide **68** to produce products **231** and **232** with a 70% yield. Compounds **231** and **232** were also found to be in a 1.2:1 diastereomeric ratio. Compounds **231** and **232** also possessed similar structural data to compounds **229** and **230**. The compounds **231** and **232** were inseparable by HPLC like their counterparts compounds **229** and **230**, however, the main difference was found in their ^{1}H NMR and ^{13}C NMR spectra. Compounds **231** and **232** had an extra proton signal at 2.90 ppm (H_3C-9''', H_3C-9') in their ^{1}H NMR spectrum representing the methyl ether protons. The ^{13}C NMR spectrum possessed an extra two carbon atom signals at 52.28 ppm (C-14'''') and 52.06 ppm (C-14') again representing the two methyl ether carbon atoms.

2.2.2 Conjugate Addition to tert-Butanesulfinyl Imines

Due to the inseparability of the imine diastereomers, the mixtures of compounds **229** and **230** as well as of compounds **231** and **232** were submitted to conjugate addition reactions with an organolithium reagent and with a Grignard reagent in an attempt to produce compounds **233**, **234**, **235** and **236** (Figure 112). The results are summarized in Table 29.



a) MeLi, THF, -78°C. b) MeMgBr, THF, -78°C.

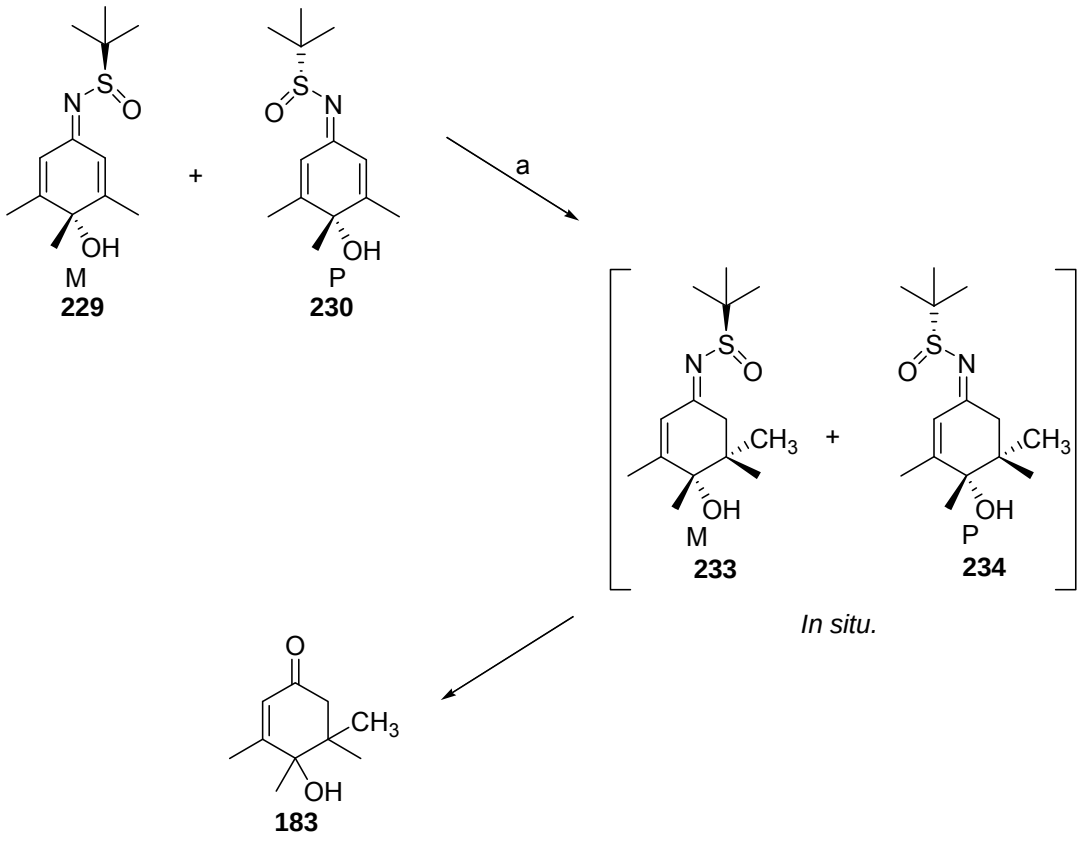
Figure 107. Conjugate addition reactions to diastereomeric mixtures.

Table 28. Grignard addition to chiral sulfinyl imine mixtures.

Entry	Sulfinyl Imine Mixture	Alkylating Reagent	t (h)	Yield (%)[a]	er[b]
1	**229** and **230**	MeLi	5	NR	--
2	**229** and **230**	CH_3MgBr	5	45	60:40
3	**229** and **230**	CD_3MgI	5	40	60:40
4	**231** and **232**	CH_3MgBr	24	NR	--

[a]Isolated yield of hydrolyzed imine. [b]er of hydrolysed imine was measured by chiral HPLC ((R,R) Whelk-01).

In an attempt to repeat the conditions published by Ellman[82] using MeLi, no reaction was observed (Table 29, Entry 1). The diastereomeric mixture of compounds **229** and **230** only reacted successfully with a Grignard reagent. However, compounds **233** and **234** were not isolated. Instead, hydrolysis product **183** was obtained in a modest yield of 45% and 20% ee (Table 29, Entry 2). Compounds **229** and **230** likely reacted with MeMgBr to form *in situ* intermediate compounds **233** and **234** that were then hydrolyzed upon work-up to form compound **183** (Figure 113).



a) CH_3MgBr, THF, -78°C.

Figure 108. Conjugate addition to diastereomeric mixtures to produce **183**.

Using deuterium labeled MeMgBr, a Grignard addition reaction was performed (Table 29, entry 3) with the diastereomeric mixture of compounds **229** and **230** was performed. The ^1H NMR displayed the same result as previously discussed when performing a Grignard addition reaction to **165**. The spectrum showed the complete disappearance of one methyl peak (Figure 114). This suggested that the hydroxyl moieties of compounds **229** and **230** were assisting the Grignard reagent to produce facial selectivity.

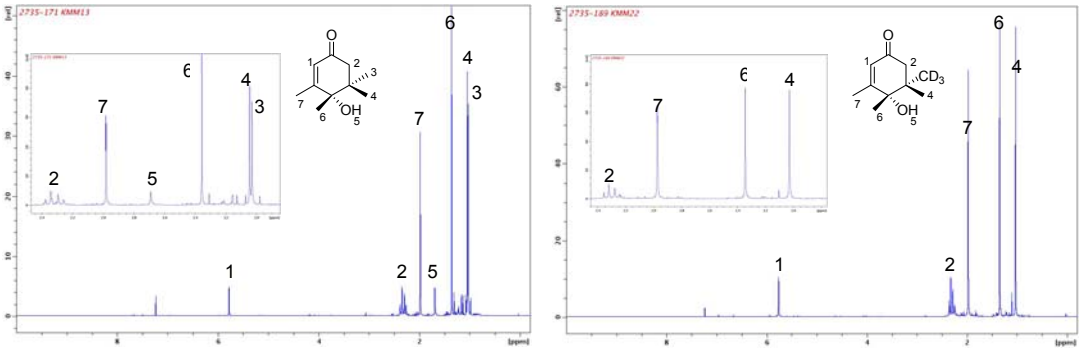


Figure 109. ^{1}H NMR comparison of **183** and deuterium labeled **184**.

The Grignard addition reaction appeared to have functioned by the use of the oxygen of the hydroxyl group assisting the addition of the Grignard reagent. Thus, the facial assistance of a Grignard reagent with conformer **229** as well as with conformer **230** was modeled (Figure 115 and 116). The model of the Grignard addition to compound **229** appeared to be unhindered by the tert-butyl moiety. The addition of the Grignard reagent could likely occur to either side of the diene ring. Thus, a Grignard addition reaction to compound **229** would likely be unselective. However, the model of the Grignard addition to compound **230** appears to be hindered on one side of the diene ring by the *tert*-butyl moiety. The addition of the Grignard reagent would likely favour one side of the dienone ring. Thus, a Grignard addition reaction to compound **230** would likely be selective. The poor selectivity achieved in the conjugate addition to the mixture of compounds **229** and **230** is perhaps indicative of both conformers reacting. If the rates of addition to each diasteromer were identical and compound **230** was the major imine (1.2:1) from the beginning synthesis of the *tert*-butanesulfinylimine mixture, then it can be calculated using an additive effect and the fact that the *tert*-butyl moiety is hindering one side of the diene ring to produce a product ratio of 1:2.6. However, if compound **230** was the minor imine (1:1.2) from the beginning synthesis of the *tert*-butanesulfinylimine mixture then it can be calculated that the tert-butyl moiety is hindering one side of the diene ring to produce a product ratio of 1:4.

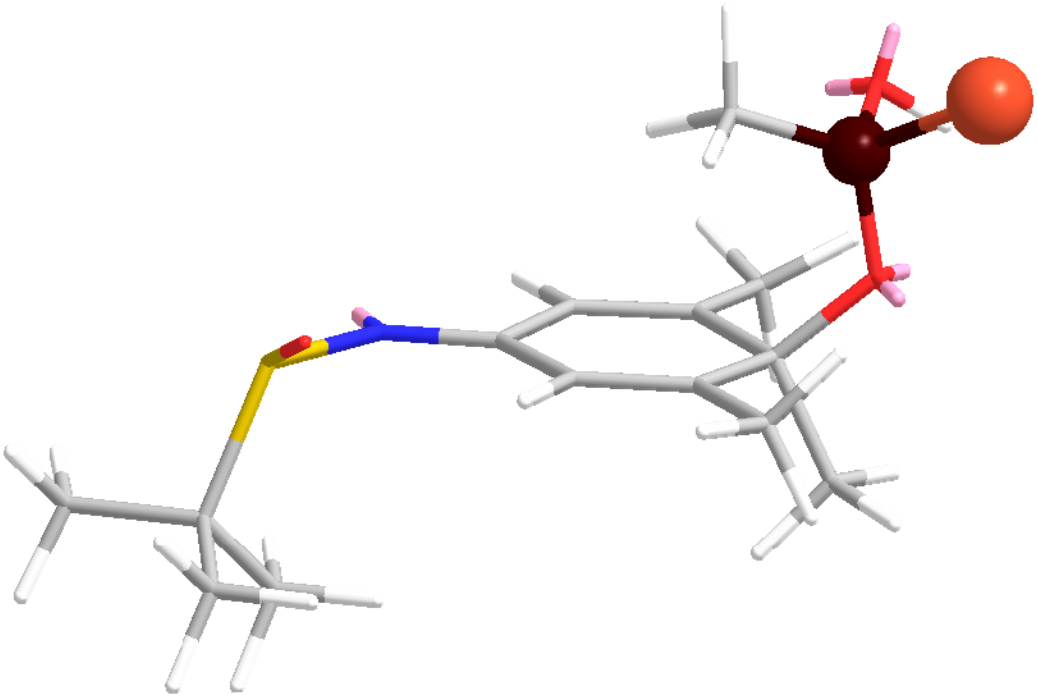


Figure 110. Modeled Grignard addition to compound **229**.

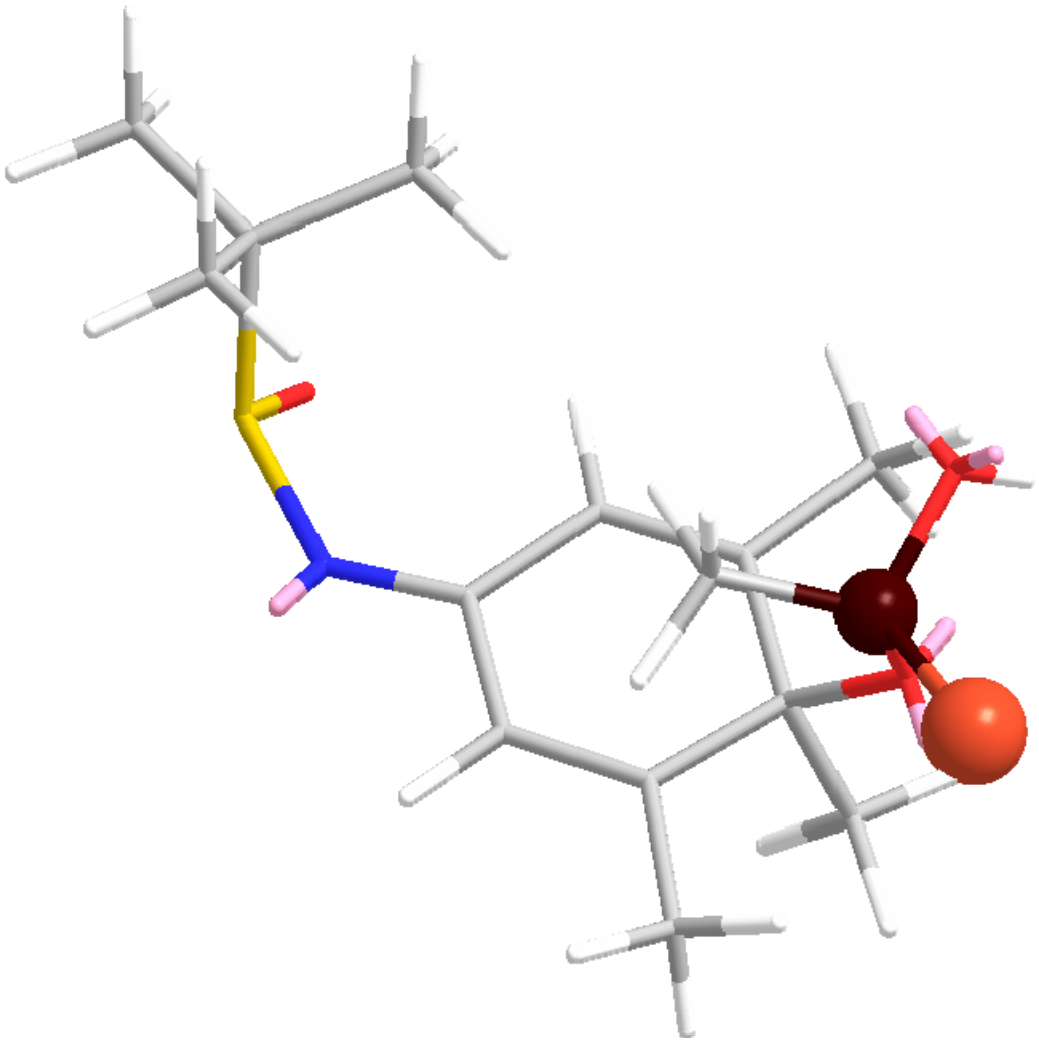


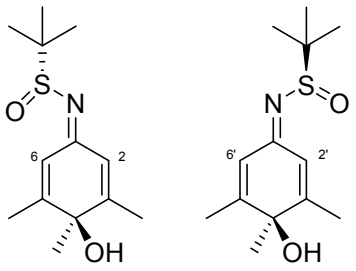
Figure 111. Modeled Grignard addition to compound **230**.

Chirality transfer or asymmetric induction from chiral catalysts or chiral auxiliaries is the basis for asymmetric synthesis of enantiomerically enriched chiral molecules.[157] The efficiency of the chirality transfer is largely dependent on how tight the interaction is between the chirality source and the reacting site. A short distance is normally considered being favorable for highly efficient chirality transfer or asymmetric induction[154]. It is of interest to study stereocontrol among remote sites.[155] In this study compounds **229** and **230** each possess an axis of chirality along with a stereocenter whose configuration is fixed. However, after the conjugate

addition reaction, the product **183** possessed a new stereocenter with a loss to the axis of chirality present in compounds **229** and **230**. As a result, a transfer of axial to central chirality occurred. Normally, axial to central chirality transfers are separated by two bond lengths.[155-156] The chirality transfer that occurred in this system is over four bond lengths. Although chirality transfer over large bond distances is rare, one recent extreme example reported by Clayden and co-workers illustrated the state of art in achieving remote stereocontrol in two sites separated by more than twenty bond lengths or a linear distance of >2.5 nm.[155] Nonetheless few cases of a chirality transfer over two bond lengths have been reported.[156]

2.2.3 Sulfinyl Imine C=N Bond Rotation Study

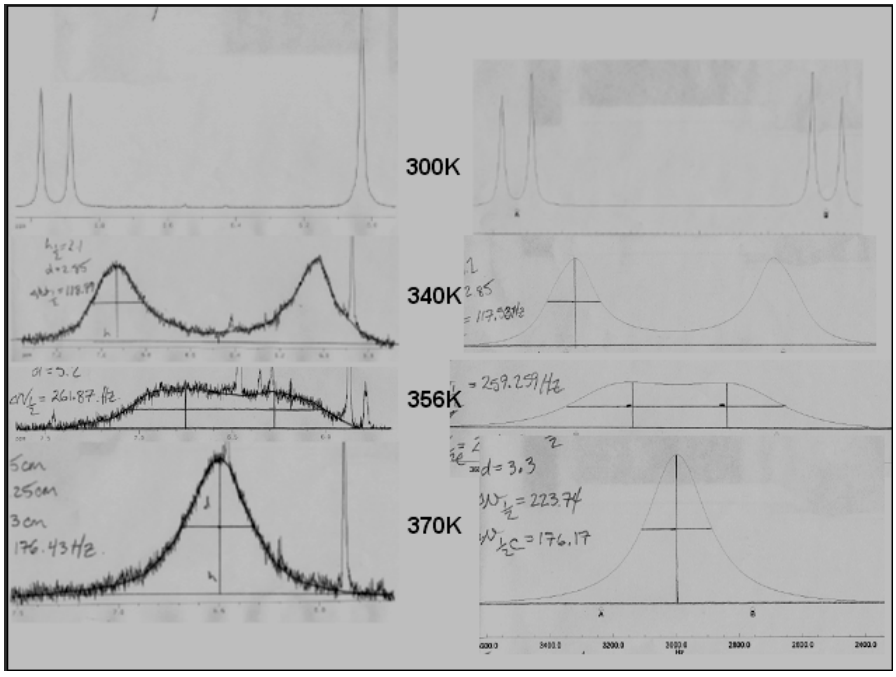
The dynamic internal motions of organic imines have been a source of interest leading to numerous NMR spectroscopic studies since the 1950s.[157] The unique property of **229** and **230** is that the C=N bond has two diastereomeric orientations: a t-butyl group anti to the hydroxyl substituent, t_{anti}, and a t-butyl group syn to the hydroxyl substituent, t_{syn} (Figure 107). The poor selectivity afforded during the conjugate addition reaction to the mixture of **229** and **230** indicated that perhaps there was an interconversion of the C=N bond issue between compounds **229** and **230**.



230 t_{anti} **229** t_{syn}

Figure 112. Two orientations of the C=N bond.

As a result, an ^{1}H NMR variable temperature experiment was performed with a sample of **229** and **230** in DMSO. The olefinic proton 2, 2', 6 and 6' peaks (Figure 108) were observed to slowly broaden and become one peak at 356 K. The resulting spectrum can then be modeled and simulated using the computer program WinDNMR (Figure 109). The computer simulation then calculates a rate constant k by measuring the line width of the ^{1}H NMR spectrum. The line width is the minimal obtainable peak width distance at the half-height of a peak (Figure 109).



Experimental **Simulation**

Figure 113. Variable temperature ^{1}H NMR experiment of **229** and **230** in DMSO.

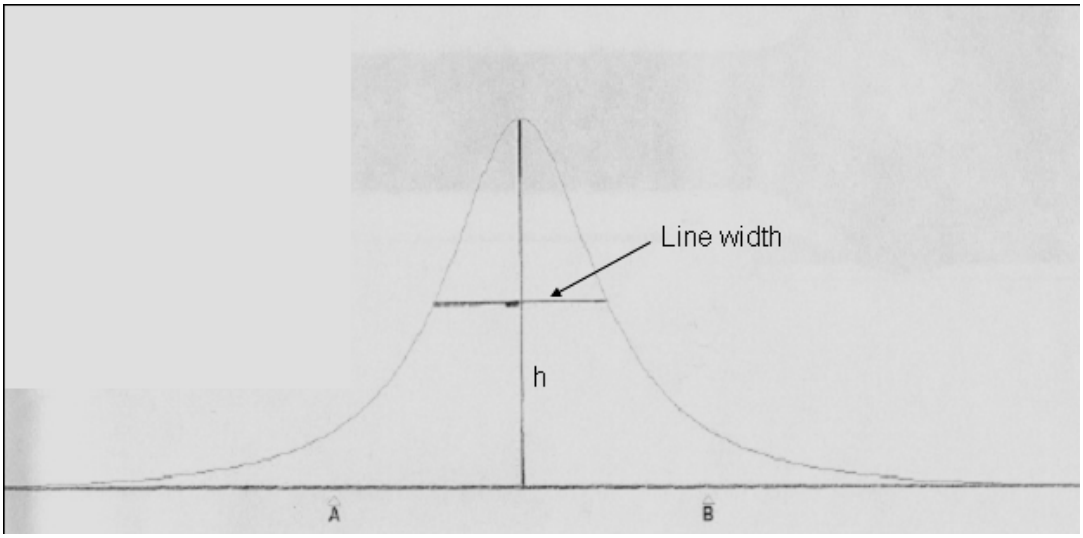


Figure 114. Line width of a simulated NMR peak.

From the values of the rate constant k a plot of ln k versus inverse temperature representing the Arrhenius equation as well as a plot of ln (k/T) versus inverse temperature representing the Eyring equation was constructed (Figure 110). Finally, the slopes and intercepts were extracted from these the plots to provide the thermodynamic parameters in Table 28.

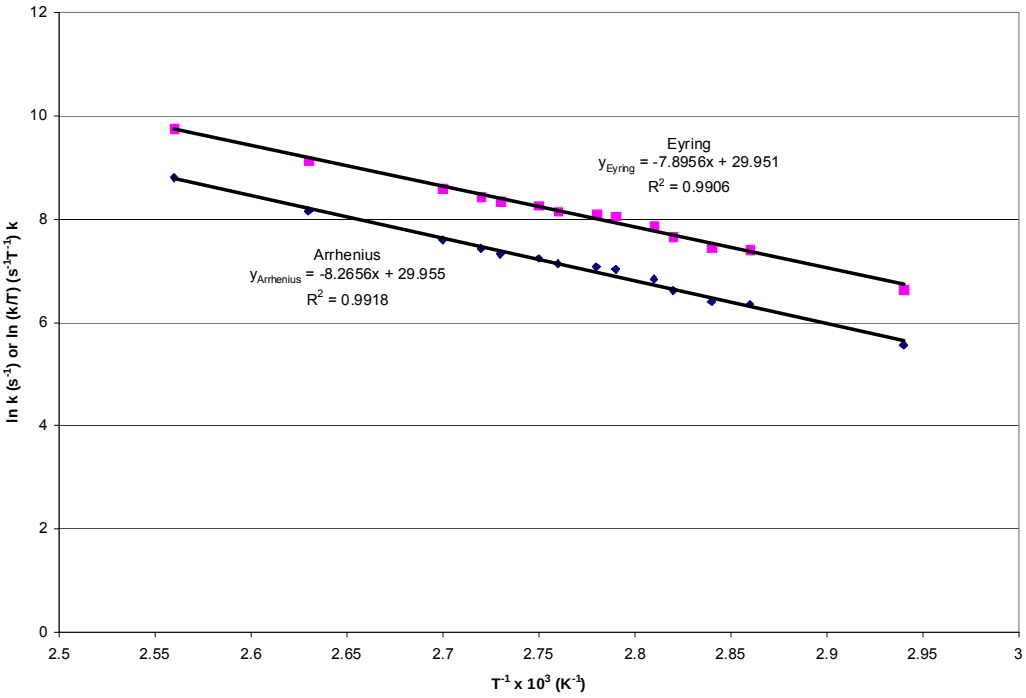
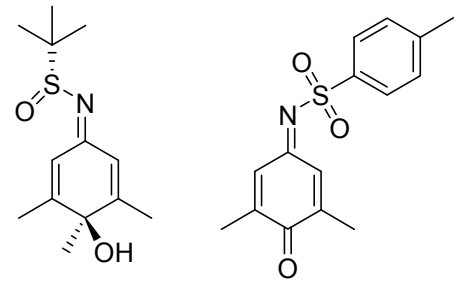


Figure 115. Arrhenius and Eyring plots.

Table 29. Thermodynamic parameters of the C=N bond within **229** and **230**.

Entry	Sample	$E_{a\ Ar}$ (kJ mol^{-1})	$\Delta H^{\ddagger}_{Ar}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{Ar}$ (J mol^{-1} K^{-1})	$\Delta G^{\ddagger}_{Ar}$ (kJ mol^{-1})
1	**229** and **230** DMSO	68.76 ± 1.83	66.28 ± 1.83	-4.22 ± 4.82	67.54 ± 1.83
Entry	**Sample**	$E_{a\ Ey}$ (kJ mol^{-1})	$\Delta H^{\ddagger}_{Ey}$ (kJ mol^{-1})	$\Delta S^{\ddagger}_{Ey}$ (J mol^{-1} K^{-1})	$\Delta G^{\ddagger}_{Ey}$ (kJ mol^{-1})
2	**229** and **230** DMSO	68.16 ± 1.83	65.68 ± 1.83	51.48 ± 5.07	50.33 ± 3.34

The E_a of rotation obtained was approximately 68 kJ mol^{-1}. However, the computed line positions depend on the level of sophistication of the theory programmed. Thus, **229** was modeled using the computer program Spartan as a comparison result. The program calculated the energy barrier of rotation of the gas phase of **229** to be 81.07 kJ mol^{-1}. The E_a of rotation value obtained was expected to be slightly lower than the modeled value since it was in the liquid state. This modeled result further supports the result E_a of rotation value obtained. Avdeenko[158] found that a similar system of N-aryl-sulfonyl-1,4-benzoquinonimines experience $\Delta G^{\ddagger}$ of rotation to be 65-80 kJ mol^{-1} (Figure 111).



229 $G^{\ddagger}$ = 50-70 KJ mol^{-1} **237** $G^{\ddagger}$ = 65-80 KJ mol^{-1}

Figure 116. $\Delta G\ddagger$ of rotation of similar systems.

The ^{1}H NMR simulation was validated in this study as the C=N bond of **229** behaved in a similar manner to that of other imines such as **211**. In addition, ^{1}H NMR simulation demonstrated that the imines **229** and **230** were interconverting approximately 222 times per second at 356 K. Therefore, a conjugate addition reaction at -78 °C will slow down the interconversion of the imines **229** and **230** to 122 times per second. In other words, the imines **229** and **230** will interconvert

once every 8.2 x 10^{-3} seconds. Therefore, although some selectivity was observed with the use of this system, there is an interconversion issue that must be considered.

2.3 Conclusion and Suggestion for Future Work

The initial work in this thesis concentrated on preparing **165** as the key substrate that could be used for the enantioselective synthsis of ABA. An ECA to **165** could act as a model system for further ECA studies with other substrates, such as **161**. Reactions using organolithium, Grignard, organozinc, organoaluminum and boronic acids were performed to **165** in order to achieve an ECA reaction. In addition, a chiral auxiliary **68** was added to **165** and used in a DCA reaction that resulted in an enantioenriched product **183**.

Attempts to perform an ECA to **165** using organolithium, Grignard, organozinc and boronic acids were unsuccessful. Two methods were developed to perform a stereoselective conjugate addition to **165**, but resulted in poor yields and moderate enantioselectivities. An ECA using an external chiral ligand **26** and triethylaluminum was successful in producing a moderate stereoselective product. The major product for most of the triethylaluminum ECA reaction trials was the (+)-syn addition stereoisomer. A DCA using a chiral auxiliary **68** was also successful in producing a moderately enantioenriched product **183**. ECA reactions using an external chiral ligand have been developed for many α,β-unsaturated carbonyl compounds. However, these ECA reactions did not extend their reaction scope to β,β-disubstituted-α,β-unsaturated carbonyl compounds. In fact, very few methods to achieve an ECA with β,β-disubstituted-α,β-unsaturated carbonyl compounds are known. In addition, even fewer methods are known to achieve an ECA with γ-substituted-β,β-disubstituted-α,β-unsaturated carbonyl compounds. Many literature works speculate as to why these compounds possess such a lack in reactivity. The main suggested reasoning for this lack of reactivity is that the extra γ and β

substituents, which add an excessive steric requirement, must be overcome in order to produce a reaction.

In order to avoid these steric issues, future experiments would be to attempt other chiral auxiliary DCA reactions that would affect the product in a diastereoselective fashion. The chiral sulfoxide moiety used by Carreno[90] is an example of a chiral moiety that could be used as an alternate chiral auxiliary strategy. In any event, the chiral auxiliary used must be one that is easily added to and removed from compound **165** and easily removed at a later stage. One could also look at new ways of performing an ECA to compound **165** by designing a new chiral external ligand. ECA reactions to γ-substituted-β,β-disubstituted-α,β-unsaturated carbonyl compounds remains a great challenge in synthetic chemistry.

Finally, a study of the dynamic motions of the C=N bond found in the structure of sulfinyl imines **229** and **230** was performed. The study used variable temperature NMR in combination with the computer software WinDNMR. As a result, the thermodynamic parameters E_a, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ of this C=N bond interconversion were calculated to be 68 kJ mol^{-1}, 66 kJ mol^{-1}, 51 kJ mol^{-1} and 50-68 kJ mol^{-1}, respectively. Therefore, the imines **229** and **230** were found to be interconverting once every 1.5 seconds at -78 °C and it was concluded that DCA reactions using this system must consider the issue of C=N bond interconversion.

CHAPTER 3: EXPERIMENTAL

3.1 General methods

All air sensitive reactions were carried out under dry argon. Tetrahydrofuran, dimethoxyethane and diethyl ether were distilled under argon from sodium and benzophenone. Dichloromethane and toluene were distilled from calcium hydride. Grignard, alkylzinc, alkylaluminum and alkyllithium reagents were obtained as stock solutions from commercial sources and used without further purification. Other chemical reagents, solvents were obtained from the Aldrich Chemical Company, Alfa Aesar, Strem Chemicals, or Frontier Scientific and used as received unless stated otherwise. All reactions were performed at least twice. Yields and selectivity measurements were reported with an accuracy of ±2%.

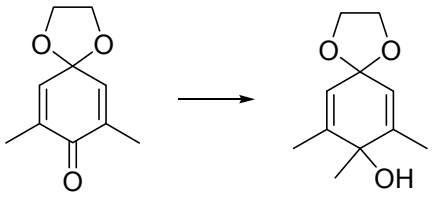
High pressure liquid chromatography (HPLC) was performed using a Hewlett Packard 1090 Series instrument. Preparative high pressure liquid chromatography (PREP HPLC) was performed using a Hewlett Packard 1100 Series instrument. HPLC separations were carried out on an (R,R)-WHELK-01 chiral column (250 mm x 4.6 mm) and a ChiralCel-OD (250 mm x 4.6 mm) chiral column, respectively. PREP HPLC separations were carried out on an (R,R)-WHELK-01 chiral column (25 cm x 21.1 mm). Flash column chromatography (FCC) was carried out using Silicycle silica gel (40-63 μm). Thin layer chromatography (TLC) was performed on precoated glass plates and precoated aluminium sheets (Merck, silica gel 60, F_{254}). Preparative thin-layer chromatography (PTLC) was carried out on glass plates (20x20 cm) precoated (0.25-1.00 mm) with silica gel 60 F_{254}. Spots on TLCs were detected using UV light (254 nm) or by immersing the TLC in a developing solution and charring the plate or sheet on a hot plate. The developing solution was prepared by dissolving concentrated sulfuric acid (35 mL), cerium (IV) sulfate (10 g) and phosphomolybdic acid hydrate (40 g) in water (1 L).

Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 500 MHz spectrometer in chloroform-d solvent unless otherwise noted. Chemical shifts are reported in ppm of δ scale with

chloroform-d (δ = 7.24 ppm for ^{1}H NMR) or (δ = 77.0 ppm for ^{13}C NMR) as the internal standard. Infrared (IR) spectra were recorded on a Biorad FTS-40 Fourier transform interferometer using a diffuse reflectance cell (DRIFT) or on a Bruker Optics Tensor 27 Spectrometer using a diffuse reflectance cell (DRIFT). In addition, only the diagnostic peak frequencies are reported. Mass spectra were performed by Ken Thoms at the Saskatchewan Structural Science Center and were recorded on a double speed VG 70-250-VSE (high resolution) and are reported as m/z ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV. Gas Chromatography/Mass Spectrometry (GC/MS) was performed on an Agilent Technologies 6890N Network GC System equipped with a 7683 Series Injector and a 5973 Network Mass Selective Detector. GC separations were carried out on a CylodexB (0.25 mm x 30 m x 0.25 μm) or a β-cyclodex (0.25 mm x 30 m x 0.25 μm) chiral column using helium at flow of 0.5 mL/min. The oven was held at 100 °C for 45 minutes and then raised to 240 °C at a rate of 10 °C/min. Optical rotations were measured on a PerkinElmer Model 341 LC Polarimeter (1 dm, 1 mL cell) at 589 nm; all concentrations are given in g/100 mL. Ultra violet (UV) spectra were recorded on a PerkinElmer Lambda 35 UV/Vis spectrometer. Melting points and boiling points are uncorrected. Melting points were measured using an electrothermal IA9000 Series digital melting point apparatus. Boiling points were measured using a Kugelrohr Buchi KGR-50 apparatus. The mass of compounds (20 mg-2 g) was reported with an accuracy of ±1 mg. (The balance used, a Mettler AE 240, Deltarange®, has reproducibility of ±0.1 mg).

3.2 Experimental Procedures and Notes

7,8,9-Trimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-ol

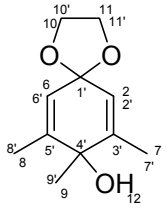


173 **174**

Method 1: 7,9-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one, **173** (10.0 g, 55.5 mmol) was dissolved in dry tetrahydrofuran (200 mL) at room temperature. The solution was then cooled to -78 °C and methyllithium (37 mL, 55.5 mmol), as a complex with lithium bromide, was added dropwise. In some cases TMEDA (7 mL, 55.5 mmol) was then added to the solution dropwise. The reaction mixture was left stirring for two hours and then quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL), dried over Na_2SO_4 (5.0 g), and concentrated under vacuum. The crude product was then dissolved in ethyl acetate (50 mL) and recrystallized with the addition of hexanes (250 mL). The white needles that precipitated were collected by filtration and washed with chilled hexane (200 mL), affording product **174** as an off-white solid (9.8 g, 90%).

Method 2: Anhydrous $CeCl_3$ (371 mg, 1.5 mmol) was placed in a 25 mL round-bottomed flask equipped with a magnetic stir bar. Next, dry tetrahydrofuran (5 mL) was added and the suspension was stirred overnight at room temperature to ensure that most of the $CeCl_3$ was dissolved. The newly formed white slurry was cooled to 0 °C and methyllithium (0.57 mL, 1.5 mmol), as a complex with lithium bromide, was added dropwise. Following the addition of MeLi, the solution was left stirring for 90 min. In a second 25 mL round bottom flask, 7,9-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one **173** (180 mg, 1.0 mmol) was dissolved in tetrahydrofuran (10 mL). The dienone solution was then cannulated to the cooled (0 °C) cerium chloride suspension. After 30 min, the reaction was quenched with 10% aqueous acetic acid (1 mL) and washed with brine (5 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL), dried over Na_2SO_4 (5.0 g), and

concentrated under vacuum. FCC chromatography (hexane/AcOEt gradient) gave the product **174** as an off-white solid (185 mg, 90%).



174

mp: 84-86°C.

IR (NaCl) ν_{max}: 3384 (OH), 2986 (CH), 1668 (CO); 1617 (C=C) cm^{-1}.

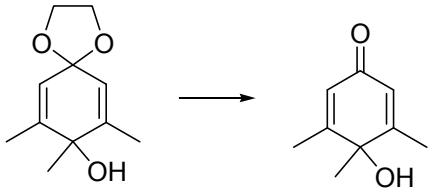
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.46 (2H, s, HC-6, HC-2), 3.97 (4H, s, H_2C-10, H_2C-11), 1.86 (6H, s, H_3C-7, H_3C-8), 1.28 (3H, s, H_3C-9).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 144.96 (s, C-2', C-6'), 125.74(s, C-1'), 122.20(s, C-3', C-5'), 100.59(s, C-4'), 64.75 (s, C-10', C-11'), 24.68 (s, C-9'), 17.34 (s, C-7', C-8').

HRMS (EI+): calcd. for $C_{11}H_{16}O_3$ $(M)^+$: 196.1099; found 196.1099.

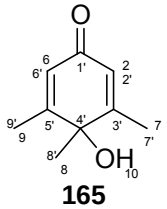
UV-Vis (MeOH): (λ_{max}, ε): 205 nm, 1.4 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-Hydroxy-3,4,5-trimethyl-2,5-cyclohexadien-1-one



174 **165**

Compound **174** (5.0 g, 25.5 mmol) was dissolved in tetrahydrofuran (200 mL) in a 500 mL round-bottomed flask equipped with a magnetic stir bar. Next, 10% aqueous hydrochloric acid (50 mL) was added to the solution. After stirring the solution at room temperature for 24 hours, the reaction was diluted with water (50 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The organic layers were collected, dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. FCC chromatography (hexane/AcOEt gradient) gave the product **165** as a a light brownish solid (3.8 g, 98%).



165

mp: 75-78°C.

IR (NaCl) ν_{max}: 3408 (OH), 2988 (CH), 1669 (CO), 1618 (C=C) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.96 (2H, s, HC-2, HC-6), 2.08 (6H, s, H_3C-7, H_3C-9), 1.59 (1H, s, HO-10); 1.42 (3H, s, H_3C-8).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 186.05 (s, C-1'), 164.38 (s, C-3', C-5'), 125.31 (s, C-2', C-6'), 71.38 (s, C-4'), 25.89 (s, C-8'), 18.19 (s, C-7', C-9').

HRMS (EI+): calcd. for $C_9H_{12}O_2$ $(M)^+$: 152.0837; found 152.0839.

UV-Vis (MeOH): (λ_{max}, ε): 237 nm, 1.3 x 10^4 $M^{-1}\cdot cm^{-1}$.

Procedure A. Representative procedure for Cu-Catalyzed conjugate addition of alkyllithium reagents.

In a 50 mL Schlenk flask equipped with a magnetic stir bar, (-)-sparteine **28** (1.8 equiv.) was dissolved in freshly distilled toluene (5 mL) and cooled to -78 °C. Next, MeLi (2.6 equiv.) as a complex with lithium bromide was added, drop wise. In a second 50 mL Schlenk flask equipped with a magnetic stir bar, the enone (1 equiv.) was dissolved in freshly distilled toluene (5 mL) and cooled to -78 °C. After the solutions were stirred at -78 °C for 30 minutes, the solution containing the enone was added dropwise to the MeLi solution. The newly formed reaction mixture was then stirred for two hours. Work-up consisted of addition of MeOH (1.0 mL) and extraction with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 (5.0 g) and concentrated under vacuum.

Procedure B. Representative procedure for Cu-Catalyzed conjugate addition of Grignard reagents.

In a 50 mL round-bottomed flask equipped with a magnetic stir bar, a mixture of CuCl (5 mol%) and the chiral ligand Taniaphos **32** (6 mol%) was dissolved in Et_2O (2.5 ml). After stirring under argon at room temperature for thirty minutes the enone (1 equiv.) dissolved in Et_2O was added dropwise. After additional stirring for ten minutes, the corresponding Grignard reagent (1.1 equiv) in Et_2O was added dropwise and the solution was stirred for 2-5 hours. The work-up consisted of the addition of saturated ammonium chloride (3.0 mL) to quench the reaction. The reaction mixture was then warmed to room temperature and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. The recovered crude product was purified by chromatography (hexane/AcOEt). The racemates were prepared using Grignard reagent solutions (5 equiv.) in THF at -78ºC.

Procedure C. Representative procedure for Cu-Catalyzed conjugate addition of dialkylzinc reagents.

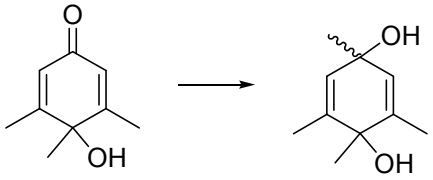
In a 50 mL Schlenk flask equipped with a magnetic stir bar, a Cu salt (2 mol%) and the chiral ligand **26** (5 mol%) were added under an inert atmosphere. PhMe (2 mL) was then added to the Schlenk flask to wash down any residual solids to the bottom. The reaction mixture was allowed to stir at room temperature for thirty minutes and then cooled to -78ºC. The alkylzinc reagent solution (1.1 M) in PhMe was then added to the Schlenk flask dropwise, and the resulting solution stirred for five min. A solution of enone (1.0 equiv) in PhMe (2 mL) was then added dropwise. The reaction mixture was allowed to warm up slowly to -30 ºC. After eighteen hours of stirring, work up consisted of the addition of 5% HCl and Et_2O to quench the reaction mixture. The reaction mixture was then extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. The recovered crude product was purified by chromatography (hexane/AcOEt). The racemates were prepared using Grignard reagent solutions (5 equiv.) in THF at -78 ºC.

Procedure D. Representative procedure for Cu-Catalyzed conjugate addition of trialkylaluminum reagents.

A 50 mL Schlenk flask equipped with a magnetic stir bar was charged with a Cu salt (2 mol%) and a chiral ligand **26** (4 mol%). Diethyl ether (2 mL) was then added and the mixture was stirred at room temperature for thirty minutes before being cooled to -30 ºC. Trimethylaluminum (1.0 mL, 2.0 M) solution in heptane was added dropwise at such a rate that the temperature did not rise above -30 ºC, and the reaction mixture was stirred at -30 ºC for a further five minutes before the enone (1 equiv.) in diethyl ether (0.5 mL) was added dropwise. Once the addition was complete the reaction mixture was raised to -15 ºC and held overnight. The reaction was quenched at -15 ºC by the addition of MeOH (0.5 mL) and then water. The reaction mixture was then extracted with diethyl ether (3 x 20 mL). The combined

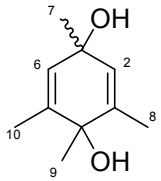
organic layers were dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. The recovered crude product was purified by chromatography (hexane/AcOEt). The racemates were prepared using Grignard reagent solutions (5 equiv.) in THF at -78 ºC.

1,2,4,6-Tetramethyl-2,5-cyclohexadiene-1,4-diol



165 **182**

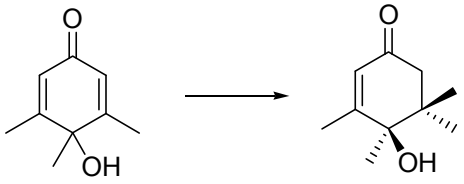
Procedure A was followed for the addition to compound **165**. Compound **165** (100 mg, 0.65 mmol) was then added as the electrophile. The recovered crude product was found to be a mixture of starting material and a mixture of 1,2 addition diastereomeric products **182** (72.5 mg, 65%). The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced a mixture of decomposed products (26 mg).



182

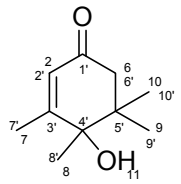
^{1}H NMR δ: 5.38 (2H, s, HC-2, HC-6); 1.85 (6H, s, H_3C-8, H_3C-10); 1.19 (6H, s, H_3C-7, H_3C-9); 1.15 (6H, s, H_3C-7, H_3C-9).

4-Hydroxy-3,4,5,5-tetramethyl-2-cyclohexen-1-one



165 **(±) 183**

Procedure B was followed for the addition to compound **165**. Compound **165** (100 mg, 0.65 mmol) was then added as the electrophile. Methylmagnesium bromide (1.1 mL, 3.0 M) in Et_2O was added dropwise and the solution was stirred for 5 hours. The recovered crude product was purified by PTLC (hexane/AcOEt 3:1) and produced product **183** as a white solid (71 mg, 65%). Optical purity was determined by chiral HPLC analysis in comparison with authentic racemic material (3% ee; (R,R)-WHELK-01 chiral column, 95:5 Hexanes:*i*-PrOH, 27°C, 1.5 mL/min).



183

mp: 79-83°C.

IR (NaCl) ν_{max}: 3393 (OH); 2970 (CH); 1643 (CO) cm^{-1}.

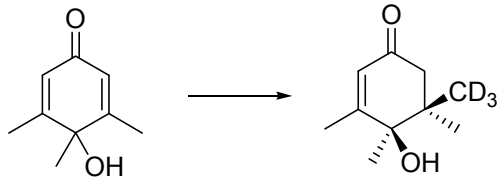
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.79 (1H, s, HC-2), 2.36 (1H, d, *J* = 17.1 Hz, HC-6), 2.31 (1H, d, *J* = 17.1 Hz, HC-6), 2.00 (3H, s, H_3C-7), 1.55 (1H, s, HO-11), 1.37 (3H, s, H_3C-8), 1.06 (3H, s, H_3C-9), 1.05 (3H, s, H_3C-10).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 197.95 (s, C-1'), 165.50 (s, C-3'), 125.98 (s, C-2'), 50.18 (s, C-4'), 40.80 (s, C-6'), 29.70 (s, C-5'), 23.84 (s, C-8'), 22.88 (s, C-9'), 22.58 (s, C-10'), 19.18 (s, C-7').

HRMS (EI+): calcd. for $C_{10}H_{16}O_2$ $(M)^+$: 168.1150; found 168.1150.

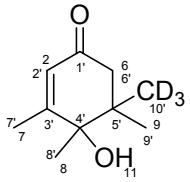
UV-Vis (MeOH): (λ_{max}, ε): 235 nm, 1.4 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-Hydroxy-3,4,5,5-tetramethyl-2-cyclohexen-1-one-d_3



165 **(±) 184**

Procedure B was followed for the addition to compound **165**. Compound **165** (100 mg, 0.65 mmol) was then added as the electrophile. Methyl-d_3-magnesium iodide (3.2 mL, 1.0 M) in Et_2O was added dropwise and the solution was stirred for five hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and afforded product **184** as a white solid (62 mg, 55%).



184

mp: 80-84°C.

IR (NaCl) ν_{max}: 3395 (OH); 2966 (CH); 1644 (CO) cm^{-1}.

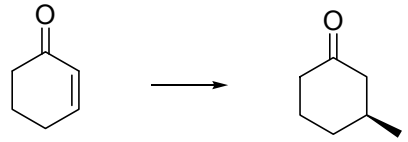
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.76 (1H, s, HC-2), 2.32 (1H, d, *J* = 17.1 Hz, HC-6), 2.28 (1H, d, *J* = 17.1 Hz, HC-6), 1.97 (3H, s, H_3C-7), 1.34 (3H, s, H_3C-8), 1.03 (3H, s, H_3C-9).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 198.31 (s, C-1'), 166.28 (s, C-3'), 125.71 (s, C-2'), 50.03 (s, C-4'), 40.54 (s, C-6'), 29.61 (s, C-5'), 24.38 (s, C-8'), 23.71 (s, C-9'), 22.43 (s, C-10'), 20.50 (s, C-7').

HRMS (EI+): calcd. for $C_{10}H_{13}D_3O_2$ $(M+H)^+$: 172.1339; found 172.1411.

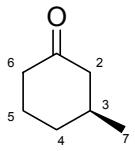
UV-Vis (MeOH): (λ_{max}, ε): 236 nm, 1.4 x 10^4 $M^{-1}\cdot cm^{-1}$.

3-Methylcyclohexan-1-one



3 **31**

Procedure B was followed for the addition to compound **3**. Compound **3** (24 μL, 0.25 mmol) was then added as the electrophile. Methylmagnesium bromide (1.1 mL, 3.0 M) in Et_2O was added dropwise and the solution was stirred for two hours. The recovered crude product was purified by bulb to bulb distillation producing a yellow oil product **31** (25 mg, 80%). Optical purity was determined by chiral GC analysis in comparison with authentic racemic material (89% ee; CyclodexB chiral column, 100 °C, 0.5 mL/min).



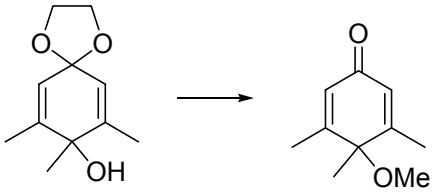
31

bp: 167-169°C at 750 torr, lit. 167-170°C.[39]

ee 89%; lit. 88%.[39]

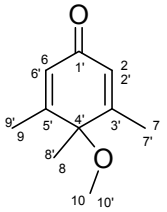
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 2.42-2.19 (4H, m, H_2C-2, H_2C-6), 2.10-1.83 (1H, m, HC-3), 1.70-1.64 (3H, m, H_2C-4, H_2C-5), 1.36 (1H, m, H_2C-4), 1.02 (3H, d, J = 6.3 Hz, H_3C-7).

4-Methoxy-3,4,5-trimethyl-2,5-cyclohexadien-1-one



174 **197**

Compound **174** (4.0 g, 20.4 mmol) was dissolved in freshly distilled tetrahydrofuran (100 mL) and cooled to –78 °C. Methyllithium (13.6 mL, 1.5 M) as a complex with lithium bromide was added dropwise to the solution. The solution was then stirred for 30 minutes. Afterwards, the solution was warmed to 0 °C and an excess of iodomethane (12.7 mL, 0.20 mol) was added. The reaction mixture was then warmed to room temperature and left stirring overnight. The reaction was then quenched with water (10 mL). Next, the aqueous phase was extracted with diethyl ether (3 x 20 mL), dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. The crude product was purified by FCC (hexane/Et_2O 7:3) to give a mixture of **197** and a dioxaspirodiene product (2.53 g, 60%). The mixture was then dissolved in tetrahydrofuran (100 mL) and 10% hydrochloric acid (50 mL) was added. The reaction was left stirring at room temperature for 24 hours. Later, the reaction was diluted with water (50 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL), dried by filtration with Na_2SO_4 (5.0 g) and concentrated under vacuum to produce product **197** as an off-white solid (2.0 g, 60%).



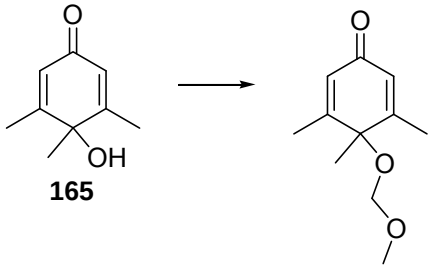
197

mp: 69-71°C, lit. 70-71°C.[141]

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 6.13 (2H, s, HC-2, HC-6), 2.92 (3H, s, H_3C-10), 1.97 (6H, s, H_3C-7, H_3C-9), 1.35 (3H, s, H_3C-8).

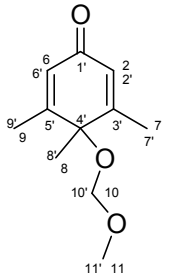
^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 185.28 (s, C-1'), 160.76 (s, C-3', C-5'), 129.17 (s, C-2', C-6'), 76.84 (s, C-4'), 52.24 (s, C-10'), 24.84 (s, C-8'), 17.68 (s, C-7', C-9').

4-Methoxymethyl-3,4,5-trimethyl-2,5-cyclohexadien-1-one



165 **198**

Sodium iodide (3.95 g, 0.26 mol) was combined with chloromethyl methyl ether (2.6 mL 34.2 mmol) in a 500 mL round-bottomed flask and dissolved in anhydrous DME (100 mL). The solution was stirred at room temperature for ten minutes. In a second 200 mL round-bottomed flask, compound **165** (1.0 g, 6.5 mmol) was combined with diisopropylethylamine (6.30 mL, 36.2 mmol) and dissolved in DME (100 mL). The second solution was stirred at room temperature for one hour. Next, the first solution was added to the second solution, dropwise. Afterwards, the newly formed solution was refluxed for twelve hours. The reaction was then cooled to room temperature and quenched with saturated sodium carbonate (30 mL) and water (30 mL). The aqueous phase was extracted with methylene chloride (4 x 30 mL), dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. The recovered crude product was purified by FCC (hexane/Et_2O 7:1) and produced product **198** as a colourless liquid (0.91 g, 78%).



198

bp: 40-44°C at 0.2 torr.

IR (NaCl) ν_{max}: 2993 (CH), 1674 (CO), 1635 (C=C) cm^{-1}.

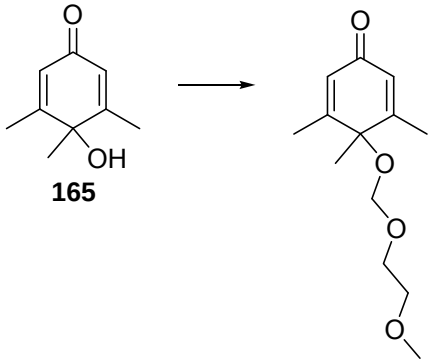
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 6.11 (2H, s, HC-6, HC-2), 4.33 (2H, s, H_2C-10), 3.39 (3H, s, H_3C-11), 2.04 (6H, s, H_3C-7, H_3C-9), 1.42 (3H, s, H_3C-8).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 185.19 (s, C-1'), 160.31 (s, C-3', C-5'), 128.47 (s, C-2', C-6'), 93.55 (s, C-10'), 76.34 (s, C-4'), 56.92 (s, C-11'), 24.77 (s, C-8'), 18.07 (s, C-7', C-9').

HRMS (EI+): calcd. for $C_{11}H_{16}O_3$ $(M)^+$: 196.1107, found 196.1107.

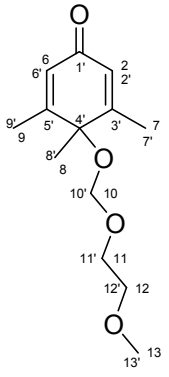
UV-Vis (MeOH): (λ_{max}, ε): 236 nm, 1.6 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-((2-Methoxyethoxy)methoxy)-3,4,5-trimethylcyclohexa-2,5-dienone



165 **199**

In a 50 mL round-bottomed flask, compound **165** (2.0 g, 13.2 mmol) was combined with diisopropylethylamine (3.44 mL, 19.7 mmol) and dissolved in DCM (10 mL). The solution was stirred at room temperature for thirty minutes. MEM chloride (2.25 mL, 19.7 mmol) was dissolved in anhydrous DCM (5 mL) in a second 50 mL round-bottomed flask. The second solution was stirred at room temperature for ten minutes. The first solution was then added to the second solution, dropwise. Afterwards, the newly formed solution was left stirring at room temperature for three hours. The reaction was then quenched with saturated sodium carbonate (20 mL) and water (20 mL). The aqueous phase was extracted with diethyl ether (4 x 30 mL), dried over Na_2SO_4 (5.0 g) and concentrated under vacuum. The recovered crude product was purified by FCC (hexane/Et_2O 5:1) and produced product **199** as a colourless liquid (1.48 g, 48%).



199

bp: 42-48°C at 0.2 torr.

IR (NaCl) ν_{max}: 2885 (CH), 1671 (CO), 1072 (CO) cm^{-1}.

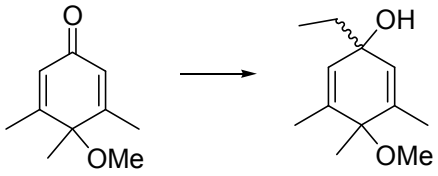
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 6.06 (2H, s, HC-2, HC-6), 4.39 (2H, s, H_2C-10), 3.66 (2H, t, J = 4.7 Hz, H_2C-12), 3.46 (2H, t, J = 4.8 Hz, H_2C-11), 3.29 (3H, s, H_3C-13), 2.04 (6H, s, H_3C-7, H_3C-9), 1.37 (3H, s, H_3C-8).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 185.09 (s, C-1'), 160.20 (s, C-3', C-5'), 128.47 (s, C-2', C-6'), 92.50 (s, C-10'), 76.35 (s, C-4'), 71.53 (s, C-12'), 68.63 (s, C-11'), 58.95 (s, C-13'), 24.74 (s, C-8'), 18.08 (s, C-7', C-9').

HRMS (CI+): calcd. for $C_{11}H_{16}O_3$ $(M+H)^+$: 241.1362, found 241.1439.

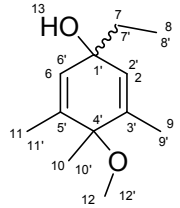
UV-Vis (MeOH): (λ_{max}, ε): 236 nm, 2.0 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-Methoxy-1-ethyl-3,4,5-trimethyl-2,5-cyclohexadien-1-ol



197 **202**

Procedure B was followed for the addition to compound **197**. Compound **197** (42 mg, 0.25 mmol) was added as the electrophile. CuCl (1.2 mg, 12.5 μmol) was used as the Cu salt. Ethylmagnesium bromide (0.29 mL, 1.0 M) in Et_2O was added dropwise and the solution was stirred for five hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced a pale yellow oil product **202** (44.2 mg, 90%).



202

bp: 42-46°C at 0.2 torr.

IR (NaCl) ν_{max}: 3423 (OH); 2971 (CH); 1066 (CO) cm^{-1}.

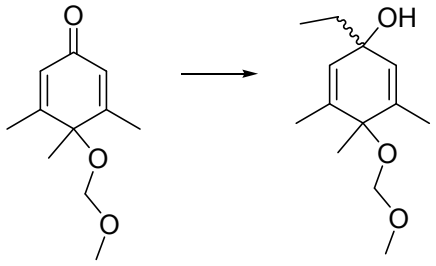
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.56 (2H, s, HC-2, HC-6), 2.88 (3H, s, H_3C-12), 1.73 (6H, s, H_3C-9, H_3C-11), 1.52 (2H, q, J = 7.5 Hz, H_2C-7), 1.22 (3H, s, H_3C-10), 0.69 (3H, t, J = 7.5 Hz, H_3C-8).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 137.23 (s, C-3', C-5'), 131.03 (s, C-2', C-6'), 75.24 (s, C-4'), 69.76 (s, C-1'), 50.89 (s, C-12'), 34.04 (s, C-7'), 24.38 (s, C-10'), 16.98 (s, C-9', C-11'), 8.72 (s, C-8').

HRMS (EI+): calcd. for $C_{10}H_{16}O_2$ $(M\text{-}H_2O)^+$: 178.1463; found 178.1356.

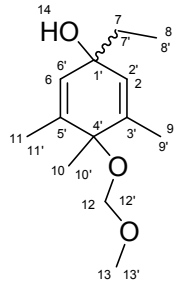
UV-Vis (MeOH): (λ_{max}, ε): 204 nm, 1.4 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-Methoxymethyl-1-ethyl-3,4,5-trimethyl-2,5-cyclohexadien-1-ol



198 **203**

Procedure B was followed for the addition to compound **198**. Compound **198** (46.8 μL, 0.25 mmol) was added as the electrophile. CuCl (1.2 mg, 12.5 μmol) was used as the Cu salt. Ethylmagnesium bromide (0.29 mL, 1.0 M) in Et_2O was added dropwise and the solution was stirred for five hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced a pale yellow oil product **203** (46.0 mg, 85%).



203

bp: 46-50°C at 0.2 torr.

IR (NaCl) ν_{max}: 3415 (OH); 2965 (CH); 1015 (CO) cm^{-1}.

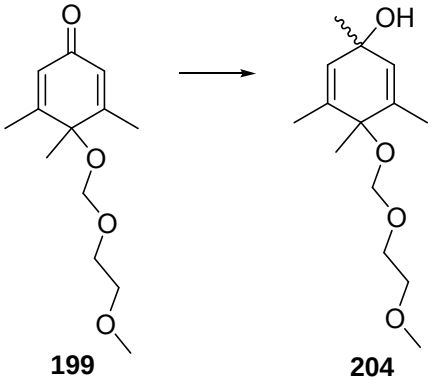
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.56 (2H, s, HC-2, HC-6), 4.42 (2H, s, H_2C-12), 3.37 (3H, s, H_3C-13), 1.80 (6H, s, H_3C-9, H_3C-11), 1.53 (2H, q, J = 7.5 Hz, H_2C-7), 1.29 (3H, s, H_3C-10), 0.70 (3H, t, J = 7.5 Hz, H_3C-8).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 137.25 (s, C-3', C-5'), 130.88 (s, C-2', C-6'), 92.64 (s, C-12'), 75.06 (s, C-4'), 69.65 (s, C-1'), 56.50 (s, C-13'), 33.88 (s, C-7'), 24.27 (s, C-10'), 17.45 (s, C-9', C-11'), 8.56 (s, C-8').

HRMS (EI+): calcd. for $C_{10}H_{16}O_2$ $(M+H)^+$: 227.1569; found 227.1284.

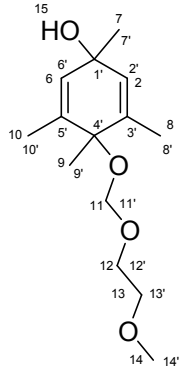
UV-Vis (MeOH): (λ_{max}, ε): 203 nm, 1.6 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-((2-Methoxyethoxy)methoxy)-1,3,4,5-tetramethylcyclohexa-2,5-dienol



199 **204**

Procedure B was followed for the addition to compound **199**. Compound **199** (60.0 μL, 0.25 mmol) was added as the electrophile. CuCl (1.2 mg, 12.5 μmol) was used as the Cu salt. Ethylmagnesium bromide (0.29 mL, 1.0 M) in Et_2O was added dropwise and the solution was stirred for five hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced a pale yellow oil product **204** (52.7 mg, 78%).



204

bp: 52-56°C at 0.2 torr.

IR (NaCl) ν_{max}: 3423 (OH); 2926 (CH); 1006 (CO) cm^{-1}.

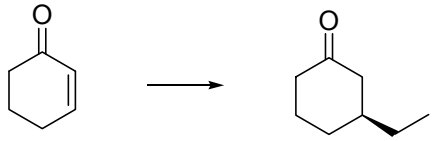
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.65 (2H, s, HC-2, HC-6), 4.51 (2H, s, H_2C-11), 3.66 (2H, t, J = 5.0 Hz, H_2C-13), 3.50 (2H, t, J = 5.0 Hz, H_2C-12), 3.31 (3H, s, H_3C-14), 1.76 (6H, s, H_3C-8, H_3C-10), 1.24 (3H, s, H_3C-9), 1.19 (3H, s, H_3C-7).

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 135.31 (s, C-3', C-5'), 132.43 (s, C-2', C-6'), 91.63 (s, C-11'), 74.95 (s, C-4'), 71.60 (s, C-13'), 67.81 (s, C-12'), 65.77 (s, C-1'), 58.96 (s, C-14'), 28.65 (s, C-7'), 24.07 (s, C-9'), 17.51 (s, C-8', C-10').

HRMS (EI+): calcd. for $C_{10}H_{16}O_2$ $(M)^+$: 256.1675; found 256.2585.

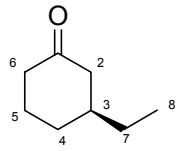
UV-Vis (MeOH): (λ_{max}, ε): 203 nm, 1.8 x 10^4 $M^{-1} \cdot cm^{-1}$.

3-Ethylcyclohexan-1-one



3 **34**

Procedure B was followed for the addition to compound **3**. Compound **3** (24 μL, 0.25 mmol) was then added as the electrophile. Ethylmagnesium bromide (1.1 mL, 3.0 M) in Et_2O was added dropwise and the solution was stirred for two hours. The recovered crude product was purified by bulb-to-bulb distillation producing a colourless liquid product **34** (25 mg, 80%). Optical purity was determined by chiral GC analysis in comparison with authentic racemic material (89% ee; CyclodexB chiral column, 100 °C, 0.5 mL/min).



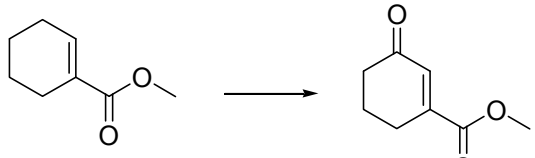
34

ee: 85%; lit. 98%.[75]

bp: 190-192°C at 750 torr, lit. 191-192°C.[75]

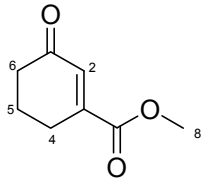
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 2.47-2.22 (4H, m, H_2C-2, H_2C-6), 2.10-1.83 (3H, m, HC-3, H_2C-5), 1.67 (2H, m, H_2C-4), 1.36 (2H, m, H_2C-7), 0.92 (3H, t, J = 7.0 Hz, H_3C-8).

Methyl 3-oxocyclohex-1-enecarboxylate



209 **75**

A 25 mL flask equipped with a stirbar was charged with compound **209** (2.0 g, 14.2 mmol), DCM (10 mL), K_2CO_3 (0.99 g, 7.1 mmol), and $Rh_2(cap)_4$ (7.1 mg, 14.2 μmol). The flask was sealed with a septum. An empty balloon was added to capture oxygen generated during the course of the reaction. Next, TBHP (14.2 mL, 71.4 mmol) was added in one portion to the flask where the colour of the solution immediately turned from light blue to deep red. Oxygen generation was observed (filling the balloon). After one hour, the solution was filtered through a short plug of silica gel to remove the catalyst. The crude product was then concentrated under vacuum. The recovered crude product was purified by FCC chromatography (hexane/Et_2O 3:1) and produced product **75** as a colourless liquid (1.98 g, 90%).

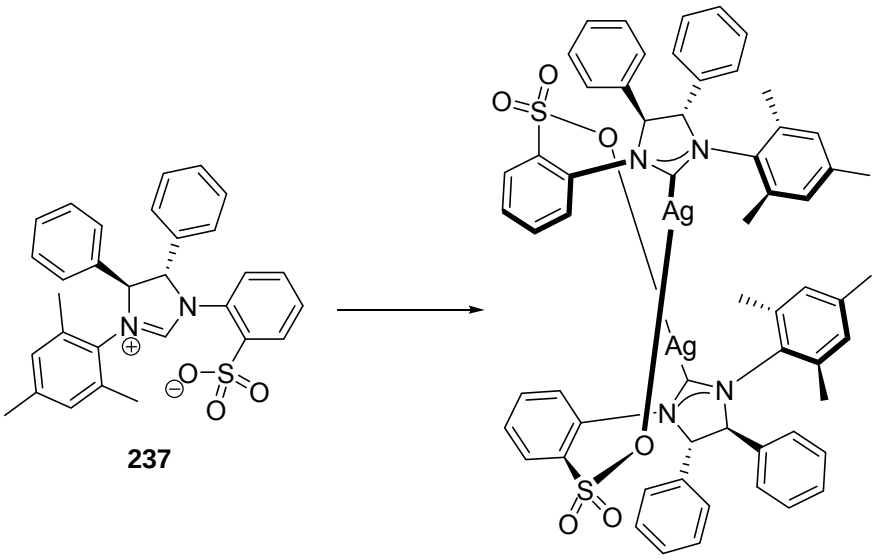


75

bp: 102-105°C at 750 torr, lit. 95-100°C.[146]

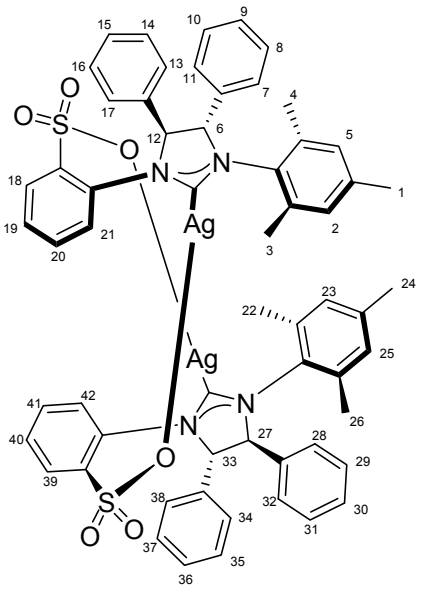
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 6.71 (1H, s, HC-2), 3.80 (3H, s, H_3C-8), 2.57 (2H, m, H_2C-6), 2.41 (2H, m, H_2C-5), 2.03 (2H, m, H_2C-4).

Ag Complex 3



237 **77**

Imidazolium salt **237** (10 mg, 0.02 mmol), Ag_2O (9.3 mg, 0.04 mmol) and 4Å MS (50 mg) were weighed out into a 10 mL round-bottomed flask. The flask was fitted with a reflux condenser, and wrapped with aluminum foil to exclude light. Tetrahydrofuran (1.0 mL) followed immediately by benzene (1.0 mL) were added to the flask, resulting in a black heterogeneous mixture. The mixture was allowed to stir at 80 °C. After three hours, the mixture was allowed to cool to room temperature. The mixture was filtered through a short plug of Celite 545 and eluted with THF (20 mL). The solution was then concentrated to produce 11.9 mg (0.02 mmol, 98.0%) of Ag complex **77** as a white solid, which was stored in the dark.[84]

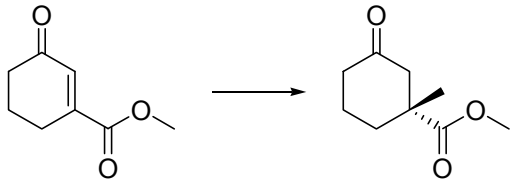


77

mp: 245-248°C, lit. 247-249°C.[84]

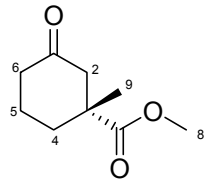
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 8.27 (2H, d, *J* = 7.3 Hz, HC-18, HC-39), 7.50−6.95 (22H, m, HC-7, HC-8, HC-9, HC-10, HC-11, HC-13, HC-14, HC-15, HC-16, HC-17, HC-20, HC-28, HC-29, HC-30, HC-31, HC-32, HC-34, HC-35, HC-36, HC-37, HC-38, HC-41), 6.80 (4H, s, HC-19, HC-21, HC-40, HC-42), 6.55 (2H, d, *J* = 10.4 Hz, HC-12, HC-33), 6.33 (4H, s, HC-5, HC-2, HC-23, HC-25), 5.18 (2H, d, *J* = 10.4 Hz, HC-6, HC-27), 2.46 (6H, s, H_3C-26, H_3C-4), 2.29 (6H, s, H_3C-22, H_3C-3), 1.42 (3H, s, H_3C-24, H_3C-1).

Methyl 1-methyl-3-oxocyclohexanecarboxylate



75 **76**

A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with chiral Ag complex **77** (2.9 mg, 4.8 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (2.4 mg, 4.8 μmol). Next, tert-butylmethylether (1.0 mL) was added to the flask. The resulting solution was allowed to stir for five minutes before being cooled to –78 °C. Dimethylzinc (0.04 mL, 0.6 mmol) was added and the resulting light yellow mixture was allowed to warm to –30 °C. After ten minutes at –30 °C, methyl 3-oxocyclohex-1-enecarboxylate **75** (30 mg, 0.2 mmol) was added to the mixture. After fifteen hours at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). The reaction vessel was allowed to warm to room temperature, where it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The resulting solution was concentrated to give a pale yellow oil that was purified by pTLC (hexane/Et_2O 3:1) and produced product **76** as a colourless liquid (27.2 mg, 82%).



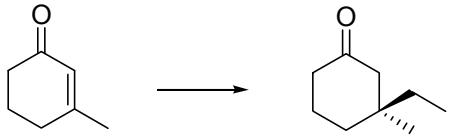
76

ee: 86%; lit. 86%.[84]

bp: 162-164°C at 750 torr.

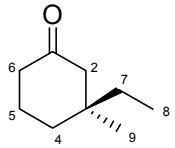
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 3.64 (3H, s, H_3C-8), 2.69 (1H, d, J = 17.0 Hz, H_2C-4), 2.14 (1H, d, J = 17.0 Hz, H_2C-4), 2.39-1.98 (2H, m, H_2C-6), 1.93-1.42 (2H, m, H_2C-5, H_2C-2), 1.24 (3H, s, H_3C-9).

3-Ethyl-3-methylcyclohexanone



24 **25**

Procedure C was followed for the addition to compound **24**. Compound **24** (97.1 mg, 0.88 mmol) was then added as the electrophile. Triethylaluminum (1.2 mL, 2.0 M) in decane was added drop-wise and the solution was stirred for eighteen hours. However, the temperature of the reaction vessel remained at -30 °C for the entire reaction time. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced product **25** as a colourless liquid (98.8 mg, 80%). Optical purity was determined by chiral GC analysis in comparison with authentic racemic material (% 68 ee; β-Cyclodex chiral column, 100 °C, 0.5 mL/min).



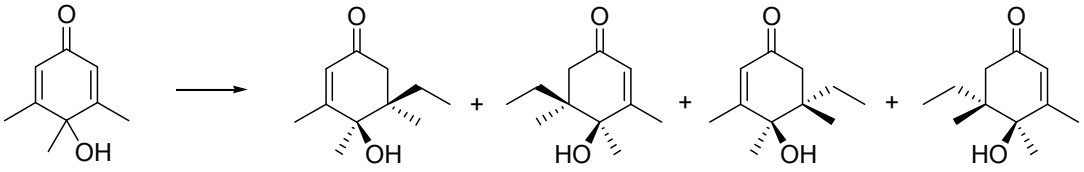
25

ee: 81%; lit. 82%.[18]

bp: 179-182°C at 750 torr.

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 2.26 (2H, t, *J* = 6.6 Hz, H_2C-6), 2.16 (1H, d, *J* = 13.6 Hz, HC-2), 2.08 (1H, d, *J* = 13.6 Hz, HC-2), 1.85 (2H, m, H_2C-5), 1.64-1.48 (2H, m, H_2C-4), 1.33 (2H, q, *J* = 7.3 Hz, H_2C-7), 0.88 (3H, s, H_3C-9), 0.83 (3H, t, *J* = 7.4 Hz, H_3C-8).

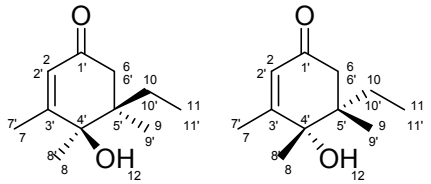
4-Hydroxy-5-ethyl-3,4,5-trimethyl-2-cyclohexen-1-one



165 **210** **211** **212** **213**

Procedure C was followed for the addition to compound **165**. Compound **165** (100 mg, 0.65 mmol) was then added as the electrophile. Triethylaluminum (1.3 mL, 2.0 M) in decane was added drop-wise and the solution was stirred for eighteen hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and afforded a mixture of products **210**, **211**, **212** and **213** as an off-white solid (16.5 mg, 15%). The ratio of products was determined by chiral HPLC analysis in comparison with authentic racemic material. ((R,R)-WHELK-01 chiral column, 80:20 Hexanes:*i*-PrOH, 27 °C, 1.5 mL/min)

The four compounds **210**, **211**, **212** and **213** were separated and collected by preparative HPLC (Figure 93). The mixture of products **210**, **211**, **212** and **213** from 20 trials were firstly pooled together. The pooled mixture of products **210**, **211**, **212** and **213** (300 mg) was weighed into a 6 mL HPLC vial. The mixture of products **210**, **211**, **212** and **213** in the HPLC vial was then dissolved in 3 mL of solvent (80:20 Hexanes:*i*-PrOH). The dissolved mixture (100 μL) was then injected into the preparative HPLC at 27 °C and at a flow rate of 1.5 mL/min. The compounds were isolated at the retention times of 13.8 min, 17.2 min, 17.9 min and 19.6 min. Lastly, the fractions from each retention time were concentrated and the optical rotations of the compounds were determined.



210 **211**

mp: 81-85°C, 81-85°C

$[\alpha]_D^{20}$: $[\alpha]_{365}^{20}$ -57 (c 0.1, $CHCl_3$), $[\alpha]_{365}^{20}$ +57 (c 0.1, $CHCl_3$)

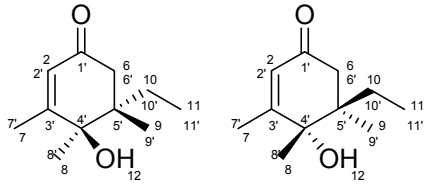
IR (NaCl) ν_{max}: 3427 (OH); 2970 (CH); 1648 (CO) cm^{-1}.

^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.77 (1H, s, HC-2), 2.38 (1H, d, *J* = 17.9 Hz, HC-6), 2.23 (1H, d, *J* = 17.9 Hz, HC-6), 1.97 (3H, s, H_3C-7), 1.54 (1H, m, H_2C-10), 1.46 (1H, m, H_2C-10) 1.36 (3H, s, H_3C-8), 0.96 (3H, s, H_3C-9), 0.77 (3H, t, *J* = 7.6 Hz, H_3C-11).

^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 197.98 (s, C-1'), 166.45 (s, C-3'), 126.23 (s, C-2'), 77.00 (s, C-4'), 45.32 (s, C-6'), 43.48 (s, C-5'), 25.87 (s, C-10'), 22.77 (s, C-8'), 19.58 (s, C-9'), 19.39 (s, C-7'), 8.61 (s, C-11').

HRMS (EI+): calcd. for $C_{11}H_{18}O_2$ $(M)^+$: 182.1307; found 182.1304.

UV-Vis (MeOH): (λ_{max}, ε): 238 nm, 1.5 x 10^4 $M^{-1}\cdot cm^{-1}$.



212 **213**

mp: 81-85°C, 81-85°C

$[\alpha]_D^{20}$: $[\alpha]_{365}^{20}$ -29 (c 0.1, $CHCl_3$), $[\alpha]_{365}^{20}$ +29 (c 0.1, $CHCl_3$)

IR (NaCl) ν_{max}: 3427 (OH); 2970 (CH); 1648 (CO) cm^{-1}.

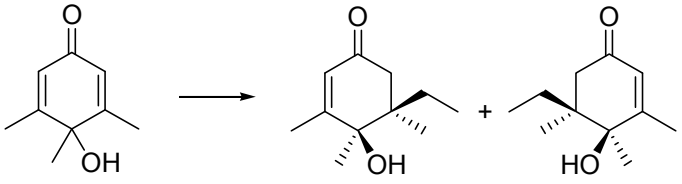
^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.80 (1H, s, HC-2), 2.39 (1H, d, *J* = 17.9 Hz, HC-6), 2.23 (1H, d, *J* = 17.9 Hz, HC-6), 1.98 (3H, s, H_3C-7), 1.55 (1H, m, H_2C-10), 1.47 (1H, m, H_2C-10) 1.37 (3H, s, H_3C-8), 0.94 (3H, s, H_3C-9), 0.79 (3H, t, *J* = 7.6 Hz, H_3C-11).

^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 197.96 (s, C-1'), 166.43 (s, C-3'), 126.23 (s, C-2'), 77.02 (s, C-4'), 45.32 (s, C-6'), 43.49 (s, C-5'), 25.87 (s, C-10'), 22.78 (s, C-8'), 19.58 (s, C-9'), 19.39 (s, C-7'), 8.62 (s, C-11').

HRMS (EI+): calcd. for $C_{11}H_{18}O_2$ $(M)^+$: 182.1307; found 182.1304.

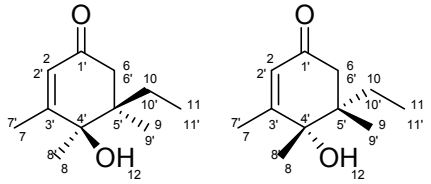
UV-Vis (MeOH): (λ_{max}, ε): 238 nm, 1.5 x 10^4 $M^{-1}\cdot cm^{-1}$.

4-Hydroxy-5-ethyl-3,4,5-trimethyl-2-cyclohexen-1-one



165 **210** **211**

Procedure B was followed for the addition to compound **165**. Compound **165** (100 mg, 0.65 mmol) was then added as the electrophile. Ethylmagnesium bromide (1.1 mL, 3.0 M) in Et_2O was added dropwise and the solution was stirred for five hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced products **210** and **211** as an off-white solid (71 mg, 65%).



210 **211**

mp: 81-85°C.

IR (NaCl) ν_{max}: 3427 (OH); 2970 (CH); 1648 (CO) cm^{-1}.

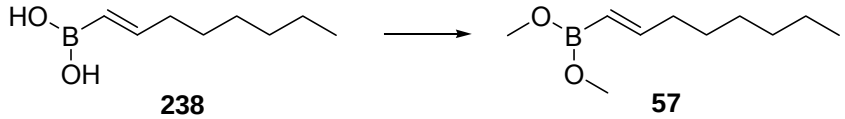
^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 5.76 (1H, s, HC-2), 2.38 (1H, d, J = 17.9 Hz, HC-6), 2.22 (1H, d, J = 17.9 Hz, HC-6), 1.96 (3H, s, H_3C-7), 1.53 (1H, m, H_2C-10), 1.45 (1H, m, H_2C-10) 1.36 (3H, s, H_3C-8), 0.95 (3H, s, H_3C-9), 0.77 (3H, t, J = 7.6 Hz, H_3C-11).

^{13}C NMR (125.75 MHz, $CDCl_3$) δ: 197.98 (s, C-1'), 166.45 (s, C-3'), 126.23 (s, C-2'), 77.00 (s, C-4'), 45.32 (s, C-6'), 43.48 (s, C-5'), 25.87 (s, C-10'), 22.77 (s, C-8'), 19.58 (s, C-9'), 19.39 (s, C-7'), 8.61 (s, C-11').

HRMS (EI+): calcd. for $C_{11}H_{18}O_2$ $(M)^+$: 182.1307; found 182.1304.

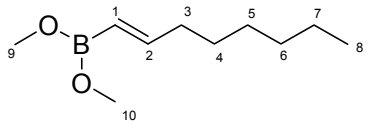
UV-Vis (MeOH): (λ_{max}, ε): 238 nm, 1.5 x 10^4 $M^{-1}\cdot cm^{-1}$.

Dimethyl oct-1-enylboronate



238 **57**

Alkenylboronic acid **238** (100 mg, 0.64 mmol) and 3Å MS (50 mg) were weighed out into a 25 mL round bottom flask. The flask was fitted with a reflux condenser and a Dean Stark trap. Methanol (2.0 mL) followed immediately by chloroform (4.8 mL) were added to the flask. The mixture was allowed to stir at reflux for 48 hours. Later, the mixture was allowed to cool to room temperature. The crude product was concentrated and purified by bulb-to-bulb distillation, producing a colourless oil product **57** (108 mg, 92%).

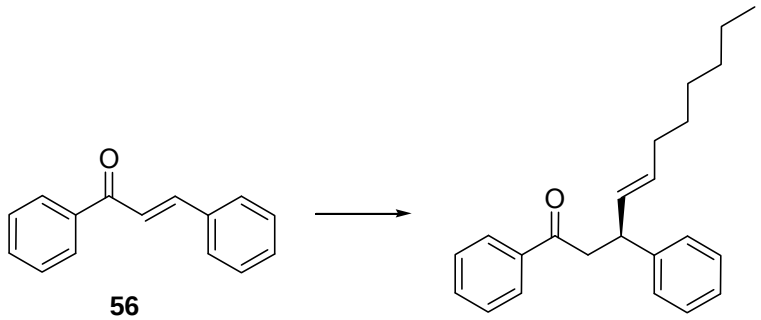


57

bp: 162-165°C at 750 torr.

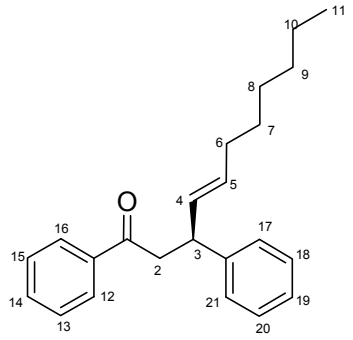
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 6.52 (1H, m, HC-2), 5.55 (1H, m, HC-1), 3.59 (3H, s, H_3C-10), 3.58 (3H, s, H_3C-9), 2.20-2.12 (m, H_2C-3), 1.90-0.98 (8H, m, H_2C-4, H_2C-5, H_2C-6, H_2C-7), 0.86 (3H, s, H_3C-8).

1,3-Diphenylundec-4-en-1-one



56 **59**

Compound **56** (20 mg, 0.1 mmol), chiral diol **58** (4.4 mg, 0.01 mmol) and 4Å MS (100 mg) were weighed out into a 25 mL round bottom flask. The flask was fitted with a reflux condenser. Next, DCM (6 mL) and alkenylboronic ester **57** (55 mg, 0.3 mmol) were added to the flask at room temperature. The mixture was brought to reflux for 12 hours. Methanol (0.5 mL) was added after the reaction was cooled to room temperature. The resulting solution was concentrated and purified by pTLC (hexane/AcOEt 3:1) and afforded product **59** as a colourless liquid (27 mg, 88%). Optical purity was determined by chiral HPLC analysis in comparison with authentic racemic material (90% ee; ChiralCel-OD chiral column, 95:5 Hexanes:*i*-PrOH, 27 °C, 1.5 mL/min)



59

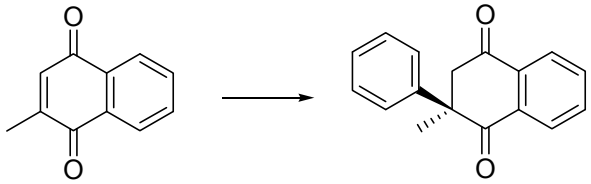
ee: 90%; lit. 98%.[77]

bp: 160-164°C at 0.2 torr.

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 7.92 (2H, d, *J* = 7.4 Hz, HC-12, HC-16), 7.53 (1H, t, *J* = 7.3 Hz, HC-14), 7.43 (2H, m, HC-13, HC-15), 7.34-7.21 (4H, m, HC-17, HC-18, HC-20, HC-21), 7.16 (1H, t, *J* = 7.3 Hz, HC-19), 5.62 (1H, dd, *J* = 15.3, 7.1 Hz, HC-4), 5.43 (1H, dt, *J* = 15.3, 7.0 Hz, HC-5), 4.07 (1H, q, *J* = 7.1 Hz, HC-3),

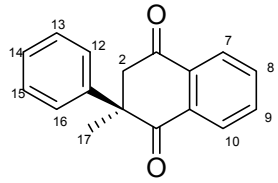
3.45-3.27 (2H, m, H_2C-2), 1.96 (2H, q, J = 6.9 Hz, H_2C-6), 1.35-1.13 (8H, m, H_2C-7, H_2C-8, H_2C-9, H_2C-10), 0.86 (3H, t, J = 7.0 Hz, H_3C-11).

2,3-Dihydro-2-methyl-2-phenylnaphthalene-1,4-dione



102 **103**

$[RhCl(C_2H_4)_2]_2$ (0.6 mg, 2.9 μmol) and (*R*)-binap (1.9 mg, 3.1 μmol) were weighed out into a 10 mL round-bottomed flask. Next, 1,4-dioxane (1 mL) was added to the flask and the newly formed solution was stirred for fifteen minutes at room temperature. $PhB(OH)_2$ (42.5 mg, 0.35 mmol) and KOH (58 μL, 58 μmol) were then added to the flask and the resulting solution was stirred for five minutes at room temperature. Compound **102** was then added along with an additional 1,4-dioxane (0.50 mL) to the flask and the resulting mixture was stirred for three hours at 50 °C. Later, the solution was cooled and passed through a pad of silica gel with EtOAc. The final solution was concentrated and purified by pTLC (hexane/AcOEt 3:1) to produce product **103** as a white solid (20 mg, 70%). Optical purity was determined by comparison of the optical rotations.



101

ee: 99%; lit. >99%.[91]

$[\alpha]_D^{20}$: $[\alpha]_{589}^{20}$ –30.0 (c 0.73, $CHCl_3$); lit. $[\alpha]_{589}^{20}$ –29.0 (c 0.73, $CHCl_3$).

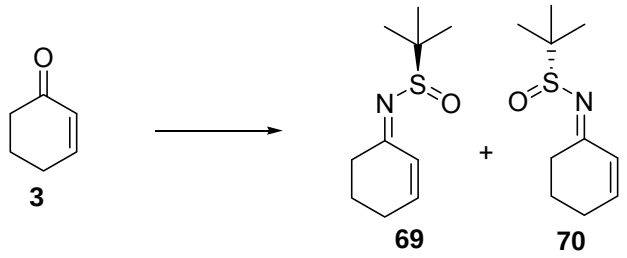
mp: 105-108°C.

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 8.03 (1H, d, *J* = 7.8 Hz, HC-7), 7.93 (1H, d, *J* = 7.7 Hz, HC-10), 7.66 (1H, m, HC-8), 7.61 (1H, m, HC-9), 7.28-7.14 (5H, m, HC-12, HC-13, HC-14, HC-15, HC-16), 3.66 (1H, d, *J* = 16.5 Hz, HC-2), 3.23 (1H, d, *J* = 16.5 Hz, HC-2), 1.63 (3H, s, H_3C-17).

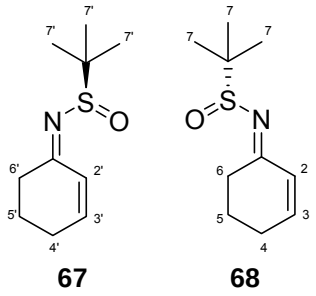
Procedure E. Representative procedure for sulfinyl imine formation.

In a 50 mL round-bottomed flask equipped with a magnetic stir bar, THF or PhMe was added to the enone (1.2 equiv) to form a 0.5 M solution. In a second 50 mL round-bottomed flask $Ti(OEt)_4$ (3.3 equiv) was combined with some solvent. Next, the solution from the first flask was added to the second flask. Tert-Butanesulfinamide (1 equiv) was then added and the resulting mixture was heated to reflux and monitored by TLC. The reaction mixture was then poured into an equal volume of saturated aqueous $NaHCO_3$ with rapid stirring and was immediately filtered through celite. The filter cake was washed with EtOAc and the aqueous layer was separated and washed once with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. The crude product was then purified by chromatography (hexane/AcOEt).

Sulfinyl Imine 1



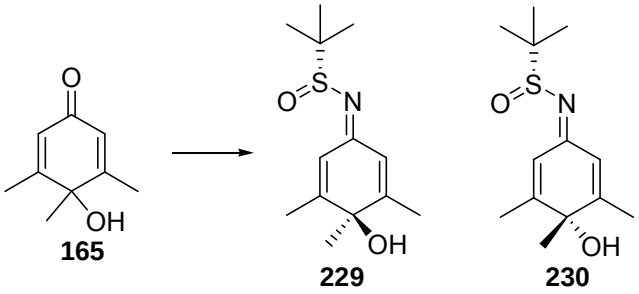
Procedure E was followed for the addition to compound **3**. Compound **3** (100 mg, 1.0 mmol) was added as the electrophile. THF (5 mL) was used as the solvent and the reaction was refluxed for 24 hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced a pale yellow oil of products **69** and **70** (170 mg, 86%).



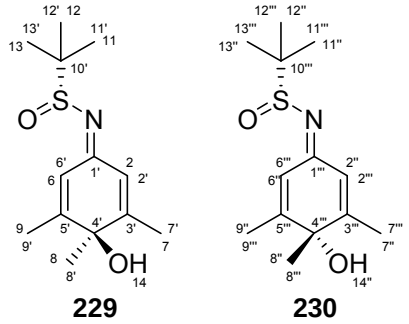
bp: 192-195°C at 750 torr, lit. 192-195°C.[82]

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 6.97 (1H, d, *J* = 10.2 Hz, HC-2'), 6.54 (2H, m, HC-3, HC-3'), 6.09 (1H, d, *J* = 10.0 Hz, HC-2), 2.89 (2H, m, H_3C-4'), 2.71 (2H, m, H_3C-4), 2.45 (2H, m, H_3C-6), 2.16 (2H, m, H_3C-6'), 1.79 (4H, m, H_3C-5, H_3C-5'), 1.11 (18H, s, H_3C-7, H_3C-7').

Sulfinyl Imine 2



Procedure E was followed for the addition to compound **165**. Compound **165** (100 mg, 0.65 mmol) was added as the electrophile. PhMe (5 mL) was used as the solvent and the reaction was refluxed for 24 hours. The recovered crude product was purified by pTLC (hexane/AcOEt 30:1) and produced a colourless oil of products **229** and **230** (67.1 mg, 40%).



bp: 102-106°C at 0.2 torr.

IR (NaCl) ν_{max}: 3283 (OH); 2978 (CH); 1543 (CN); 1043 (SO) cm^{-1}.

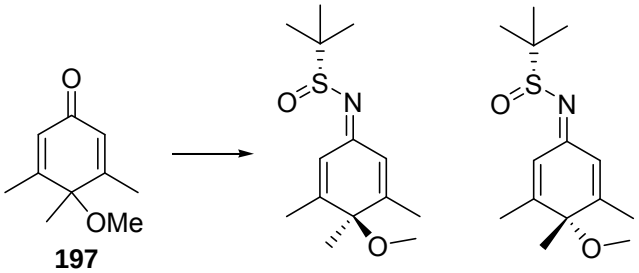
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 7.01 (1H, s, HC-6''), 6.93 (1H, s, HC-6), 6.04 (2H, s, HC-2, HC-2''), 3.31 (1H, s, HO-14''), 2.80 (1H, s, HO-14), 2.07-2.03 (12H, m, H_3C-7, H_3C-9, H_3C-7'', H_3C-9''), 1.36 (3H, s, H_3C-8), 1.35 (3H, s, H_3C-8''), 1.21 (9H, s, H_3C-11, H_3C-12, H_3C-13), 1.19 (9H, s, H_3C-11'', H_3C-12'', H_3C-13'').

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 165.40 (s, C-1'''), 164.25 (s, C-1'), 159.65 (s, C-3'''), 158.61 (s, C-3'), 157.14 (s, C-5'''), 155.80 (s, C-5'), 125.50 (s, C-6'''), 125.19 (s, C-6'), 118.11 (s, C-2'''), 117.61 (s, C-2'), 71.26 (s, C-4'''), 71.12 (s, C-4'), 57.60 (s, C-10'''), 57.07 (s, C-10'), 25.76 (s, C-8'''), 25.54 (s, C-8'), 22.90 (s, C-13''',C-13'), 22.48 (s, C-12''', C-12'), 22.26 (s, C-11''', C-11'), 18.81 (s, C-7''',C-7'), 18.07 (s, C-9'''), 17.93 (s, C-9').

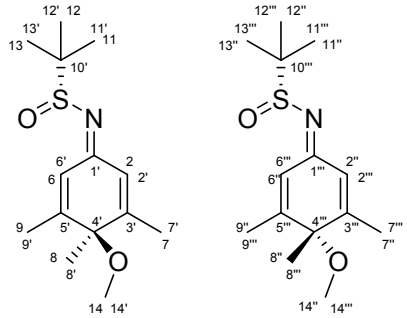
HRMS (EI+): calcd. for $C_{10}H_{16}O_2$ $(M+H)^+$: 256.1293; found 256.1378.

UV-Vis (MeOH): (λ_{max}, ε): 254 nm, 2.3 x 10^4 $M^{-1}\cdot cm^{-1}$.

Sulfinyl Imine 3



Procedure E was followed for the addition to compound **197**. Compound **197** (100 mg, 0.65 mmol) was added as the electrophile. PhMe (5 mL) was used as the solvent and the reaction was refluxed for 24 hours. The recovered crude product was purified by pTLC (hexane/AcOEt 30:1) and produced a yellow solid of products **231** and **232** (123.9 mg, 70%).



bp: 98-102°C at 0.2 torr.

IR (NaCl) ν_{max}: 3468 (OH); 2983 (CH); 1664 (CO); 1550 (CN); 1092 (SO) cm^{-1}.

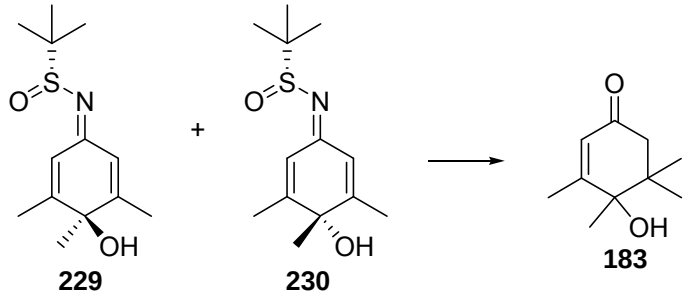
^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 7.28 (1H, s, HC-6''), 6.95 (1H, s, HC-6), 6.24 (2H, s, HC-2, HC-2''), 2.90 (6H, s, H_3C-14'', H_3C-14), 1.98-1.93 (12H, m, H_3C-7, H_3C-9, H_3C-7'', H_3C-9''), 1.33 (6H, s, H_3C-8, H_3C-8''), 1.22 (18H, s, H_3C-11, H_3C-12, H_3C-13, H_3C-11'', H_3C-12'', H_3C-13'').

^{13}C NMR (125.76 MHz, $CDCl_3$) **δ:** 164.58 (s, C-1'''), 164.18 (s, C-1'), 156.62 (s, C-3'''), 156.32 (s, C-3'), 153.67 (s, C-5'''), 153.32 (s, C-5'), 129.03 (s, C-6''', C-6'), 122.99 (s, C-2'''), 121.80 (s, C-2'), 77.00 (s, C-4''', C-4'), 57.48 (s, C-10'''), 57.33 (s, C-10'), 52.28 (s, C-14''''), 52.06 (s, C-14'), 25.22 (s, C-8'''), 24.82 (s, C-8'), 22.41 (s, C-11''',C-11', C-12''', C-12', C-13''', C-13'), 18.71 (s, C-7''',C-7'), 17.55 (s, C-9''', C-9').

HRMS (EI+): calcd. for $C_{10}H_{16}O_2$ $(M+H)^+$: 269.1449; found 269.1426.

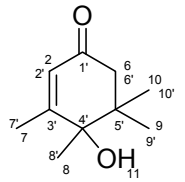
UV-Vis (MeOH): (λ_{max}, ε): 248 nm, 2.3 x 10^4 $M^{-1}\cdot cm^{-1}$.

Sulfinyl Imine 4



229 **230** **183**

Procedure B was followed for the addition to compounds **229** and **230**. The mixture of compound **229** and **230** (100 mg, 0.39 mmol) was then added as the electrophile. Methylmagnesium bromide (1.1 mL, 3.0 M) was added dropwise and the solution was stirred for five hours. The recovered crude product was purified by pTLC (hexane/AcOEt 3:1) and produced product **183** as a white solid (36.2 mg, 55%). The ratio of products was determined by chiral HPLC analysis in comparison with authentic racemic material (20% ee; (R,R)-WHELK-01 chiral column, 95:5 Hexanes:*i*-PrOH, 27 °C, 1.5 mL/min).



183

mp: 79-83°C.

^{1}H NMR (500.13 MHz, $CDCl_3$) **δ:** 5.79 (1H, s, HC-2), 2.36 (1H, d, *J* = 17.1 Hz, HC-6), 2.31 (1H, d, *J* = 17.1 Hz, HC-6), 2.00 (3H, s, H_3C-7), 1.55 (1H, s, HO-10), 1.37 (3H, s, H_3C-8), 1.06 (3H, s, H_3C-9), 1.05 (3H, s, H_3C-10).

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