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SELECTIVE METHODS FOR THE SYNTHESIS OF HIGHLY-SUBSTITUTED CYCLOPENTADIENYL AND INDENYL LIGANDS

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Doctor of Philosophy

By

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SELECTIVE METHODS FOR THE SYNTHESIS OF HIGHLY-SUBSTITUTED CYCLOPENTADIENYL AND INDENYL LIGANDS

A Dissertation APPROVED FOR THE
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

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ACKNOWLEDGMENTS

In South Africa, there is a beloved annual tradition known as the Comrades Marathon. This race between two cities is uphill one year, and downhill the next. Oddly enough, for the professional runners sometimes the downhill stretch is the most treacherous. Despite the difficulty, every year friends and family members step up to the line and run the race together as amateur marathoners. In the last hours of the race, they are all seen leaning heavily on each other as they step over the finish line. Siblings, grandparents and grandchildren, parents and their children, colleagues, and close friends encourage each other all the way through the race. The event is so well known for being a communal act, that strangers will stop to help fallen runners. Thankfully, this has been my experience in graduate school. Although I cannot possibly thank all the people who have slowed their pace to shout much appreciated encouragement along the way, I would like to thank some for running the race with me.

Thanks to Ron Halterman, your expertise, generous funding, and well placed words of encouragement made for many wonderful years of labor. A special thanks for allowing and assisting my sprint to the finish. Thanks to my husband, Phil, for the loving confidence you have placed in my abilities and the many hours of advice you have offered to help smooth my progress. Thanks to Ray Frazier, and my brothers Ken, Kristian, and Kyle. The Bible says that brothers are born for times of stress and I am so grateful to have so many brothers to lean on for support. Thanks to Eric Bailly, Ruby Rahman, Brett Behrens, and Dr. Marin, I treasure memories of working and studying beside all of you. Thanks to David and Tami Martyn for sharing the joys of your young family with me. Thanks to the members of the organic division faculty and my committee for making my successful progress through the program possible and thanks to Arlene Crawford, Laura Cornell, and Susan Alguindigue, you have all greatly increased the quality of my experience here. There are many others whom I should thank, and to whom I am deeply grateful but I would like to conclude by thanking my undergraduate adviser Daryl Cox, and my parents Ken and Linda Kaufmann for listening carefully during the year that I began to dream of running this race and for the many years that you spent preparing and encouraging me.

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ABSTRACT

Cyclopentadienes and indenes are very desirable as ligands for Group 4 metallocenes, which serve as catalysts for olefin polymerization and continue to be investigated as catalysts for other asymmetric reactions. The more regioselective synthetic methods usually generate these desirable ligands through an annelation method involving cyclization of the five-membered ring. In some instances, naturally occurring and widely available chiral molecules have been used in these annelations to create enantiomerically pure cyclopentadienes and indenes.

Since there are few examples of these desirable ring annelation methods, the object of our research has been to develop two novel ring annelation methodologies which may be applied to both indene and cyclopentadiene synthesis and allow the generation of regioselectively substituted and chiral ligands. These two methodologies are each based on versatile well-known carbon-carbon bond forming reactions. The first method intramolecularly employs a carbonyl addition known as the Nozaki-Hiyama-Kishi or Ni(II)/Cr(II) mediated coupling reaction and the second

method employs ring-closing metathesis with Grubbs' and Schrock's catalysts.

We applied the Nozaki-Hiyama-Kishi or Ni(II)/Cr(II) mediated coupling reaction in a three step approach to chiral annelated indenes from (1*R*)-(+)-camphor, (1*R*,5*S*)-(+)-nopinone, and (-)-menthone. This method involved C-alkylation of the lithium enolates of the chiral ketones with 2-bromobenzyl bromide, followed by intramolecular Ni(II)/Cr(II) mediated coupling of the aryl bromide to the ketone, and dehydration of the resultant alcohol to form the chiral annelated indenes. The camphor annelated indene and the pinanyl annelated indene were obtained as pure compounds in overall yields of 42% and 26% respectively. Epimerization during the coupling reaction of the chiral center bearing an enolizable proton caused the formation of both the *trans*- and *cis*-menthyl annelated indenes in a 2:1 mixture with an overall yield of 38%. We attempted to extend this ring-closing method to the synthesis of substituted cyclopentadienes from ketones and *(Z)*-1,3-dibromoalkenes, but encountered several difficulties.

We executed a proof of concept for the use of ring-closing metathesis with Grubbs' II and Schrock's catalyst for five-membered ring formation in the synthesis of substituted indenes, tetrahydroindenes, and cyclopentadienes. We synthesized aryl diene starting materials, 1-(1-methylethen-1-yl)-2-(prop-2-en-1-yl)-benzene and 1-(1-methylethenyl)-2-(2-methylprop-2-en-1-yl)-benzene, from 2'-chloroacetophenone through a Wittig olefination and an aryl Grignard reaction. Using these starting materials, we found that Schrock's catalyst formed the trisubstituted olefin of the five-membered ring of 1H-3-methylindene quantitatively, but did not form the tetrasubstituted olefin of 1H-2,3-dimethyl indene. We synthesized

tetrahydroindene, 1H-2-phenyl-tetrahydroindene, and the s-*trans* diene 1-phenylbicyclo[4.3.0]nona-1,5-diene from cyclohexanone in low unoptimized yields through C-alkylation with allylbromide reagents followed by addition of vinyl Grignard reagents to form olefin substituted cyclohexanols, which were ring-closed with Grubbs' II catalyst in benzene at 65-70 °C. The yields, 10-20% for ring-closure, were presumably low due to the strain involved in formation of the *trans*-fused five-membered rings of the [4.3.0] bicyclic skeletons. 3-Ethyl-4-methyl-6-phenylhept-1,6-dien-3-ol was synthesized through C-alkylation with an allylbromide reagent followed by addition of vinyl Grignard reagent to the ketone. The ring-closure of 3-ethyl-4-methyl-6-phenylhept-1,6-dien-3-ol to regioselectively form an unannelated trisubstituted cyclopentadiene, 1-ethyl-2-methyl-4-phenylcyclopenta-1,3-diene, with Grubbs' II catalyst was very facile and resulted in an unoptimized yield of 35%. We concluded that this ring-closing metathesis methodology is a promising technique for the synthesis of a variety of substituted ligands for metallocene catalysts.

Chapter 1

Desirability of Substituted Metallocene Ligands and Known Synthetic Methodologies

1.1 Desirability of Substituted Metallocene Ligands

Cyclopentadienes and indenes are very desirable as ligands for transition metals. The exceptionally strong bonds that these ligands form with transition metals make them attractive scaffolds for building chiral environments around these metals [1]. Metallocenes are desirable catalysts for the industrial production of regio- and stereoregular polypropene. In a recent and clearly illustrated comprehensive review entitled "The Selectivity in Propene Polymerization with Metallocene Catalysts," Resconi, Cavallo, Fait, and Piemontesi have critically summarized what is known about the mechanism of olefin polymerization with metallocene catalysts and the remarkable influence of catalyst design on the molecular weight and crystallinity of the polymer produced with ample examples and insightful conclusions [2]. While the ultimate usefulness of the polymer is determined by the molecular weight, the purpose for which the polymer may be used is also dependent on the degree of crystallinity the polymer exhibits. The degree of polypropene crystallinity is a result of the regio- and stereoregularity of the polymer [2]. Polymers with moderate stereoregularity

may be elastomeric, while those with higher stereoregularity will behave as "softened thermoplastics" [3]. The stereoregularity and molecular weight of the polymer is determined by the growth of the chain at the metal, so these important polymer properties may be controlled by the design of the metallocene catalyst.

A metallocene catalyst has two active coordination sites, one occupied by the growing polymer chain and the other by the olefin monomer. If a metallocene has regioselective but stereo-nonselective coordination sites, the

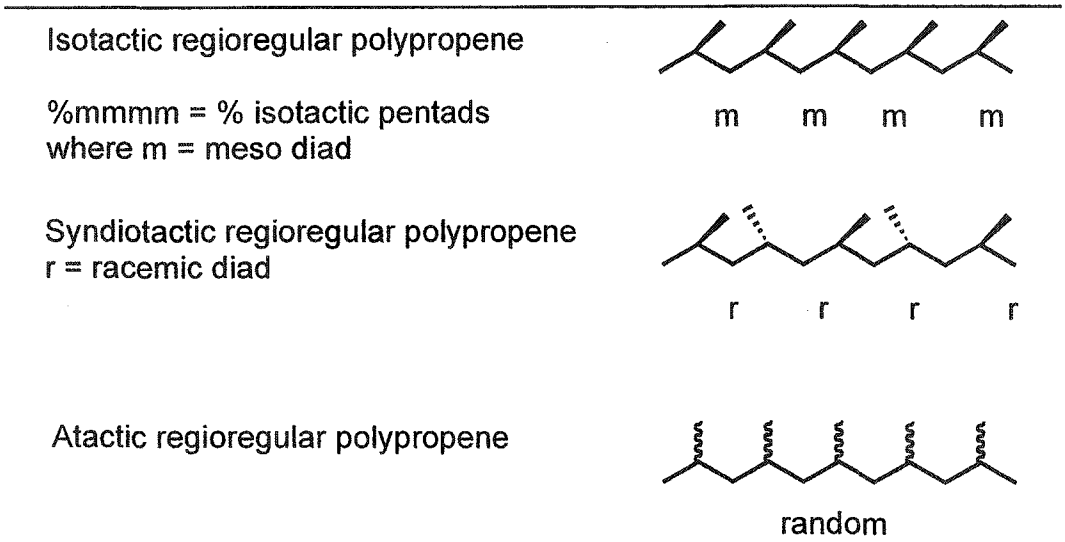


Figure 1.1 Isotactic, Syndiotactic, and Atactic Polypropene

resulting polymer will be regioregular and stereoirregular, hence an atactic and amorphous polymer (Figure 1.1). However, if a metallocene has regio- and stereoselective coordination sites, the resulting polymer will be regio- and stereoregular, hence an isotactic (or syndiotactic) partially crystalline polymer. The mechanism of propene polymerization is a "two-site, chain migratory insertion" mechanism, so both sites on the metallocene alternately serve as the enantiofacial coordination site for the propene monomer [2]. The influence of metallocene symmetry, or rather the influence of the symmetry relationship of

these two coordination sites, on the stereocontrol of polymerizations has been clearly described in a set of conventions now known as "Ewen's Symmetry Rules" [2]. For example, C_2 symmetric metallocenes may have two enantioselective sites on the metal which constitute homotopic environments, so isotactic polymers may be expected as their products.

The challenge in metallocene polymerization catalyst design is to find catalysts that give high molecular weight polymers with excellent regio- and stereocontrol. Achieving all three goals in one design has driven research into methods for the synthesis and substitution of cyclopentadienes, tetrahydroindenes, and indenes for several decades. A general understanding of the influence of substitution patterns on the indene ligands has been developed, especially in the case of chiral *ansa* C_2 symmetric metallocenes related to Brintzinger's catalyst (Figure 1.2). In these catalysts, the carbon 2, 3, and 4 positions are the three important sites of substituent variation besides the bridging unit. The effects of substituting these positions has been summarized in general terms by Resconi and coauthors as follows, if the carbon 2 position is substituted, in general, an increase in regioselectivity and stereoselectivity is observed, while if the carbon 3 position is substituted, very high regioselectivity may be observed [2]. Knowledge of the substituent effects of indenyl ligands has been developed in large part because regioselective synthetic methods are available for these ligands. The sheer variety of ligands made available through

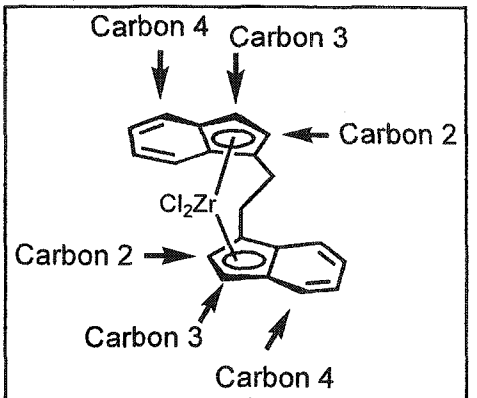
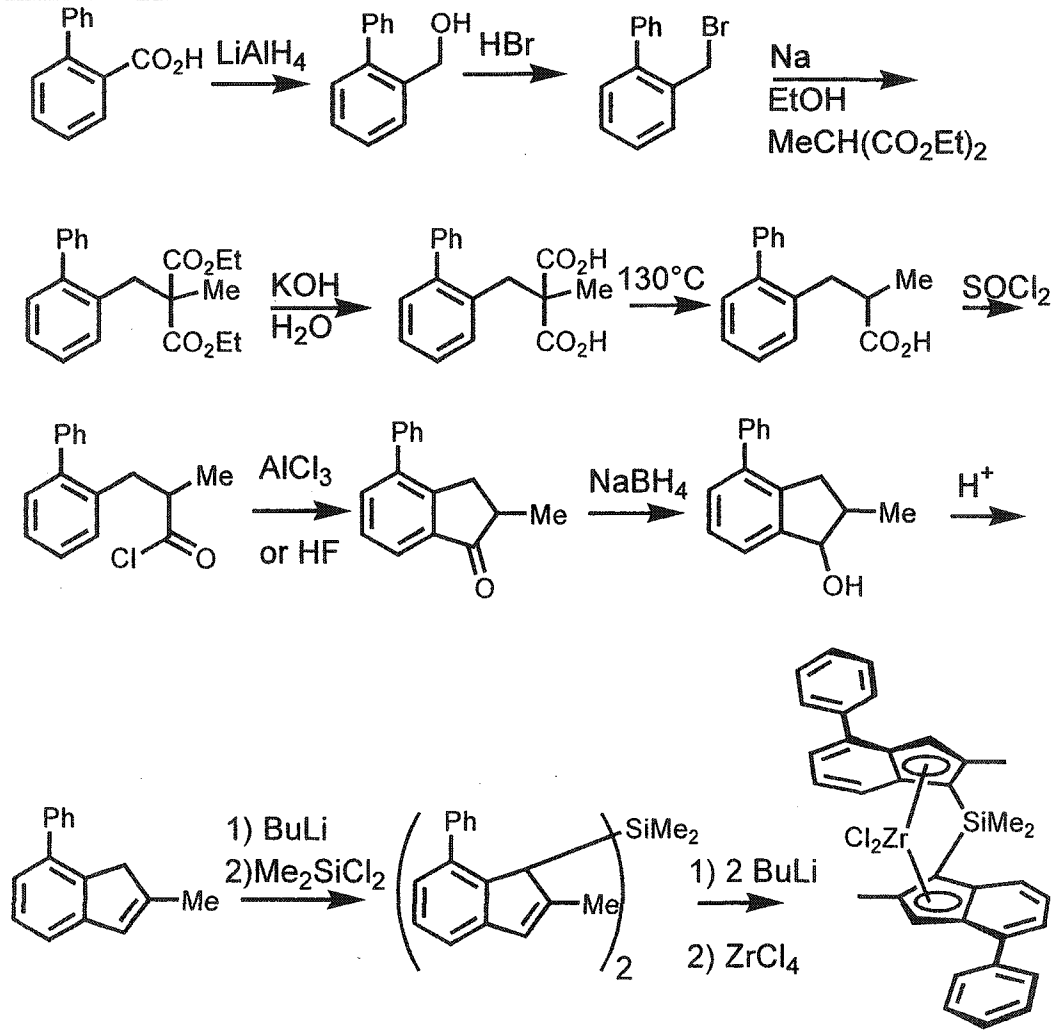


Figure 1.2 Brintzinger's Catalyst



Scheme 1.1 Synthesis of a Catalyst for the Commercial Production of Isotactic Polypropene

these methods has led to a body of knowledge useful to the continued design of high performing catalysts.

Even so, there exist very few methods for the efficient synthesis of highly substituted indene ligands from inexpensive starting materials. A prime example of this deficiency is the straightforward but lengthy synthesis of the catalyst shown in Scheme 1.1, which is used in the industrial scale production of isotactic polypropene because of the incredibly high stereocontrol it exhibits (86-99% *mmmm)* and the excellent molecular weights of the resulting polymers

(M_w=250000-730000) [2,4].

The importance of being able to vary the substituents on the ligands is driven home in an account by Waymouth of research that was conducted on conformationally dynamic indenyl metallocenes substituted in the carbon 2 position [3]. The research showed that by varying the electronic and steric demands of the substituent the metallocene conformational equilibrium could be shifted toward the chiral *anti* (*rac*) conformation, which produces isotactic polypropene, and shifted away from the achiral *syn* (*meso*) conformation, which produces atactic polypropene (Figure 1.3). Studies such as this are made possible by the availability of good synthetic methodology for the preparation of substituted metallocenes.

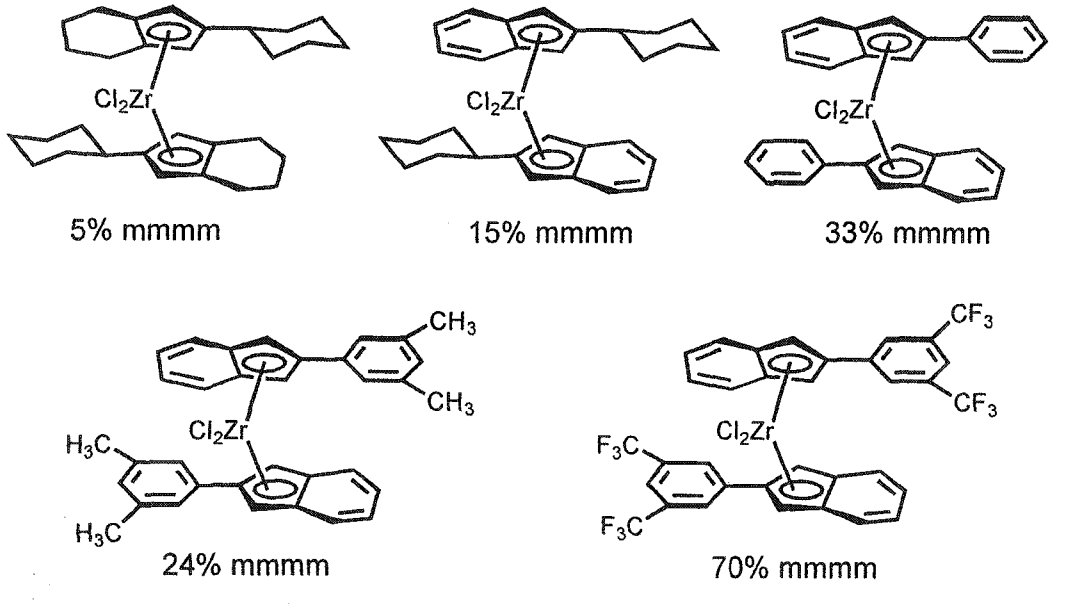
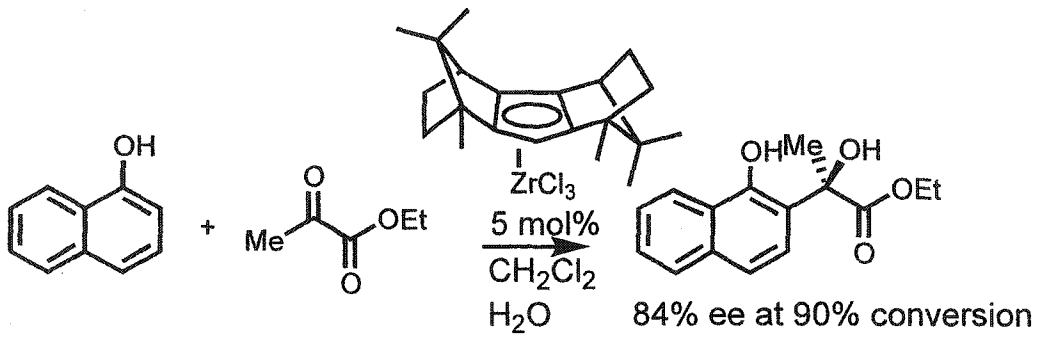


Figure 1.3 Conformationally Dynamic Metallocenes Shown in *Rac* Conformations and the Stereoregularity of the Polypropene Produced

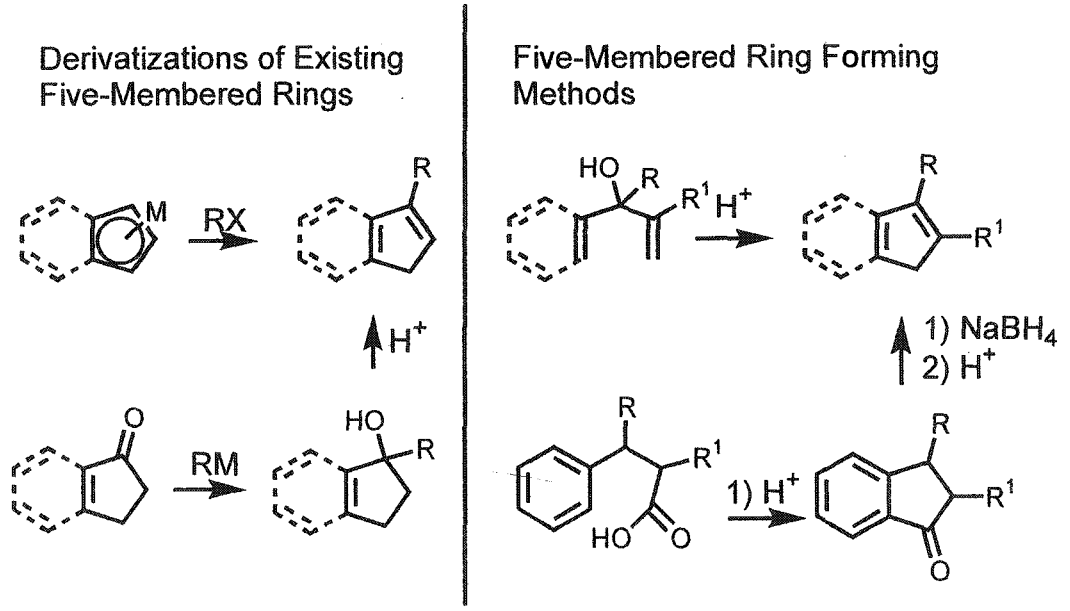


Scheme 1.2 Asymmetric Aldol-type Reaction with Chiral Catalyst

Chiral indene, cyclopentadiene, and tetrahydroindene catalysts are also being investigated for application to other asymmetric reactions of synthetic interest. An example is Erker's use of a chiral cyclopentadienyl zirconium trichloride as a Lewis acid catalyst for an aldol-type reaction (Scheme 1.2). With optimization, it was possible for them to attain an 84% e.e. at 90% conversion [5]. The scope of potential applications for chiral catalysts derived from such ligands extends beyond carbon-carbon bond formation and olefin polymerization. Group 4 metallocenes formed from highly substituted and chiral cyclopentadienes and indenes continue to be investigated as catalysts for "asymmetric alkene hydrogenations, imine and ketone reductions, and alkene epoxidations" among other asymmetric reactions [6,7].

The desirability of a wide variety of regioselectively substituted indene, cyclopentadiene, and tetrahydroindene ligands for polymerization and other asymmetric catalysis applications is incentive for continued investigation into efficient regioselective synthetic methods for the synthesis of these ligands. While a wide variety of substituted indenes and cyclopentadienes have been made available, the synthetic methods used are often harsh, at times very lengthy, and in the case of cyclopentadiene, not regioselective.

1.2 Known Methodologies

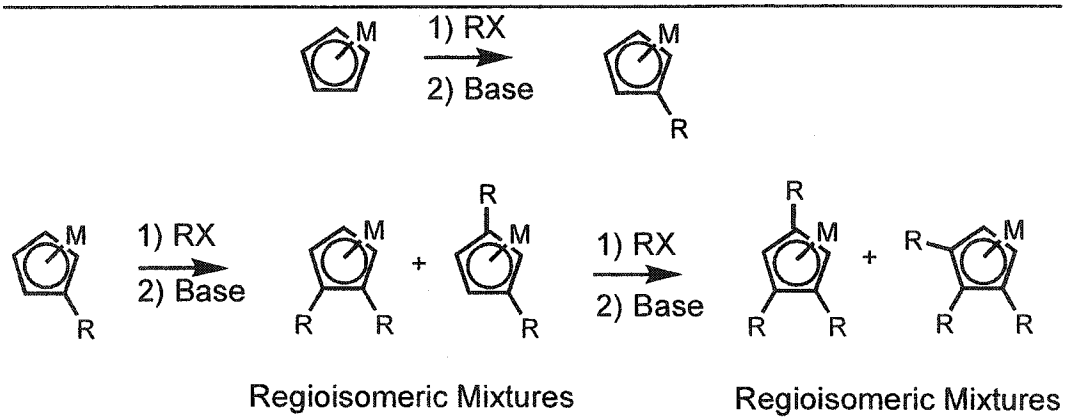


Scheme 1.3 Two Approaches to Substituted Cyclopentadienes and Indenes

In order to understand the reasons for this research into new methodologies, and to appreciate the advantages or limitations found in these new methods, it is necessary to be aware of some of the methods used in recent years to synthesize unbridged indenes and cyclopentadienes. For a more comprehensive perspective, a review article written by Ivchenko, Ivchenko, and Nifant'ev with well organized summaries of the various synthetic methodologies is recommended [8]. Interesting and illustrative recent examples are highlighted here whenever possible with an emphasis on those examples that involve highly substituted and/or chiral cyclopentadienes and indenes. The methods presented here are divided into two groups, those that involve *derivatization of existing five-membered rings* and those that are *five-membered ring forming methodologies* (Scheme 1.3).

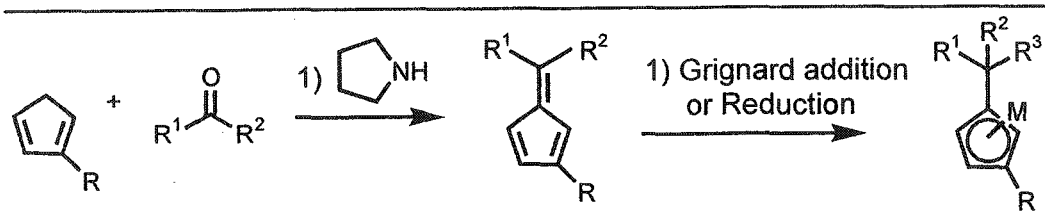
1.2.1 Cyclopentadienes: Derivatization of Existing Five-Membered Rings

The common methods for synthesis of substituted cyclopentadienes through derivatization of existing five-membered rings include direct alkylation, addition to or reduction of pentafulvenes, addition to or reduction of cyclopentenones followed by dehydration, and reduction of cyclopentadienones. For organizational purposes, we will consider tetrahydroindenes to be a subset of cyclopentadienes.



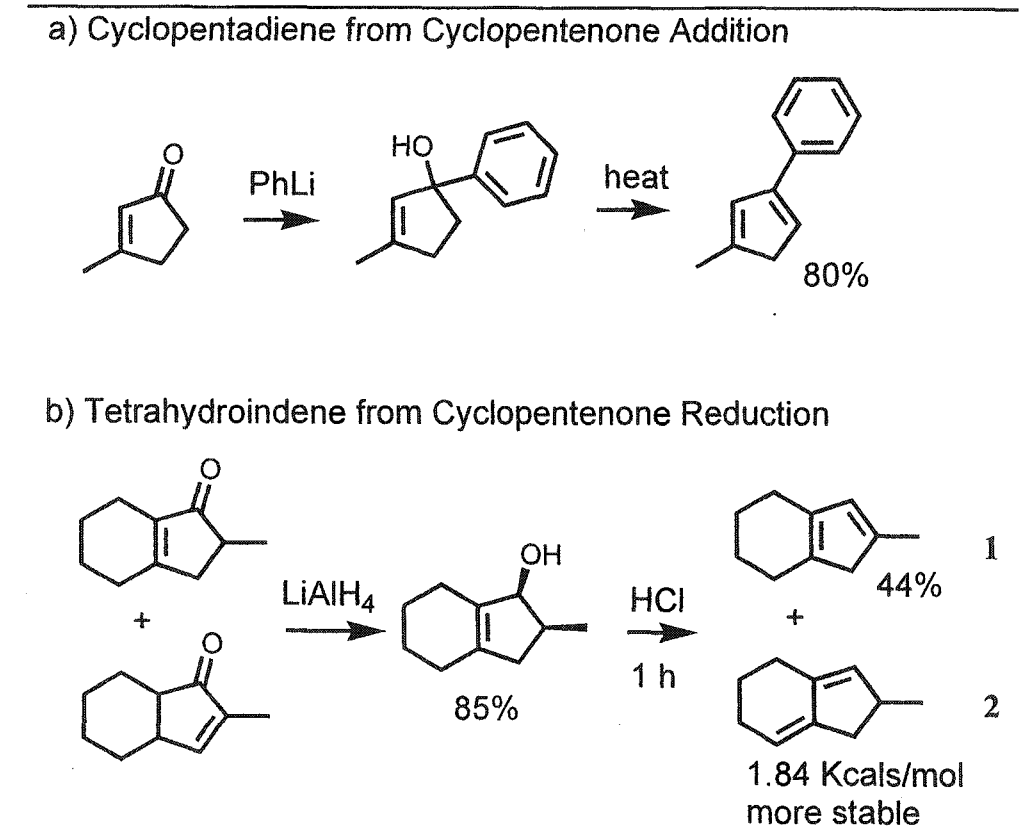
Scheme 1.4 Substitution of Cyclopentadiene by Direct Alkylation

Cyclopentadienyl anion alkylations work well for generating monoalkyl cyclopentadienes. However, when this method is used to make di- and trisubstituted cyclopentadienes, mixtures of 1,2- and 1,3-regioisomers may be expected (Scheme 1.4) [9]. Although the mixtures improve with bulkier alkyl halides, a problem with elimination instead of substitution sometimes arises [10].



Scheme 1.5 Substituted Cyclopentadiene from 6,6-Disubstituted Pentafulvene

Thus, a popular alternative when seeking to synthesize 1,3-disubstituted cyclopentadienes is through Grignard addition or reduction of 6-substituted or 6,6-disubstituted pentafulvenes, which may be obtained through condensation of ketones or aldehydes with cyclopentadienyl anion (Scheme 1.5) [11,12]. For obvious reasons, neither of these methods is suitable for attaching a phenyl substituent directly on a cyclopentadiene. Incorporation of a phenyl substituent directly on the cyclopentadiene may be achieved in good yield by



Scheme 1.6 Cyclopentadiene and Tetrahydroindene from Cyclopentenone

alkylation of a cyclopentenone with phenyl lithium followed by dehydration [8]. Cyclopentenones have also been used in the synthesis of substituted tetrahydroindenes through reduction and dehydration. However, in the case shown in Scheme 1.6, the acid catalyzed dehydration led to significant amounts of the more stable rearranged s-*trans* diene **2** [13]. Addition to or reduction of cyclopentenones is a good regioselective method for incorporation of a variety of substituents. However, in many cases, the cyclopentenones required for the synthesis of certain cyclopentadienes are not readily available and must be synthesized through low to moderate yield ring-closures, which will be considered in a later section.

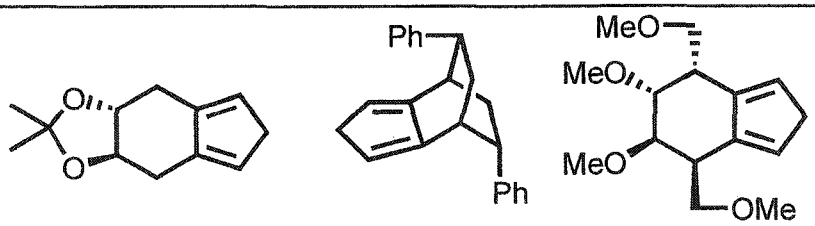
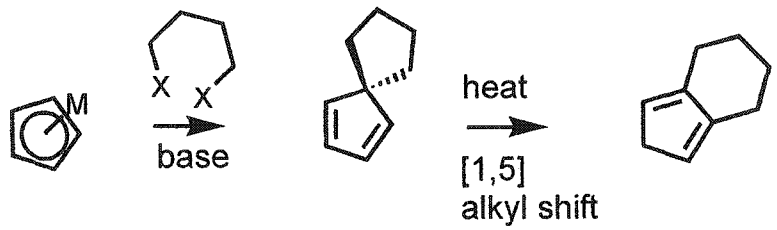


Figure 1.4 Tetrahydroindenes from Cyclopentadienyl Anion Double Alkylation

For the synthesis of chiral tetrahydroindenes such as those shown Figure 1.4, cyclopentadienyl anion double alkylation remains the standard method [14]. Although spiro compounds are formed from these double alkylations, a thermal [1,5]-sigmatropic alkyl shift achieved through gas phase pyrolysis may be



Scheme 1.7 Cyclopentadienyl Anion Double Alkylation

used to obtain the desired tetrahydroindenes (Scheme 1.7). Further substitution of tetrahydroindenes through direct alkylation of the tetrahydroindenyl anion results in a regioisomeric mixture of 1 and 2 position alkylated products.

The most common technique for the synthesis of substituted tetrahydroindenyl ligands is the hydrogenation of an indenyl metallocene. However, this technique is only useful for certain metals [13]. Clearly, more efficient and versatile regioselective methods for the synthesis of these compounds are desirable.

Thus, we have seen that methods for the synthesis of cyclopentadienes involving the derivatization of five membered rings include alkylation of cyclopentadienyl anions, a method that is generally not regioselective, and addition to cyclopentenones, a regioselective method that is limited by the accessibility of starting substrates.

1.2.2 Indenes: Derivatization of Existing Five-Membered Rings

The common methods for synthesis of substituted indenes through derivatization of existing five-membered rings include direct alkylation of indenyl anion, nickel or palladium catalyzed cross-coupling with indenyl bromide or indenyl triflate, double condensation of a 1,4 diketone with cyclopentadienyl anion, and addition to or reduction of indanones.

Through a classic procedure, alkylation of the 1 and 3 positions of the five-membered rings of indenes may be achieved through the treatment of indenyl lithium with alkyl halides or sulfonate esters (Figure 1.5) [15]. This method is unsatisfactory for bulky alkyl groups, where competing elimination reactions

lower the yields. However, an attractive alternative is the palladium or nickel catalyzed cross-coupling reaction between an indenyl triflate or bromoindene and a Grignard reagent (Scheme 1.8). This method may be used to synthesize chiral indenes substituted in either position 1 or position 2 [16].

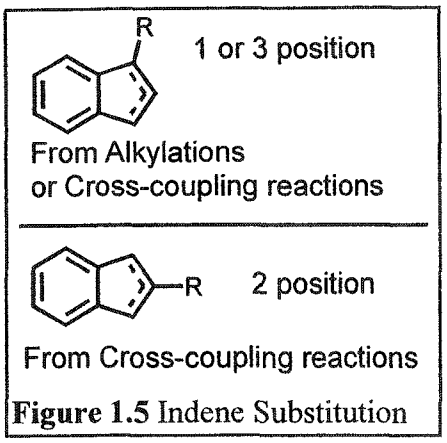
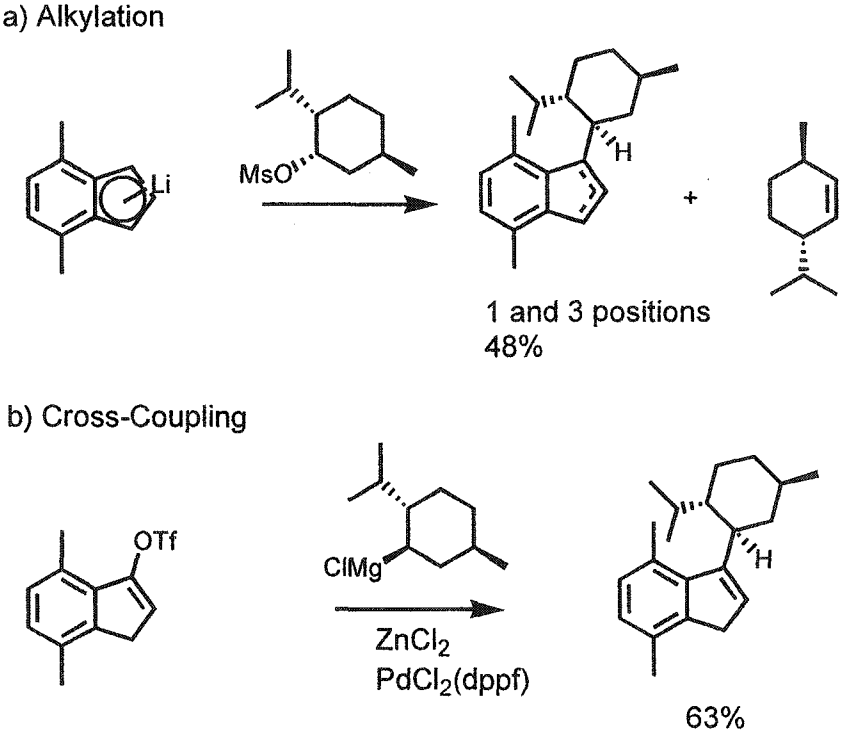


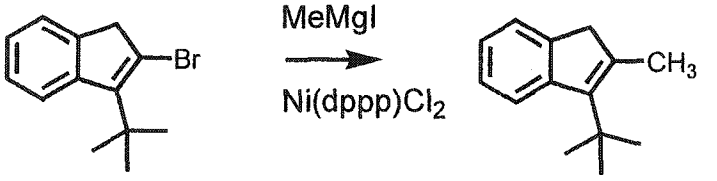
Figure 1.5 Indene Substitution



Scheme 1.8 Substitution of Indene at Positions 1 and 3

Although, especially for sterically congested syntheses, significant optimization of the coupling reaction conditions is often required, the ready availability of a wide variety of highly effective catalysts and ligands for this

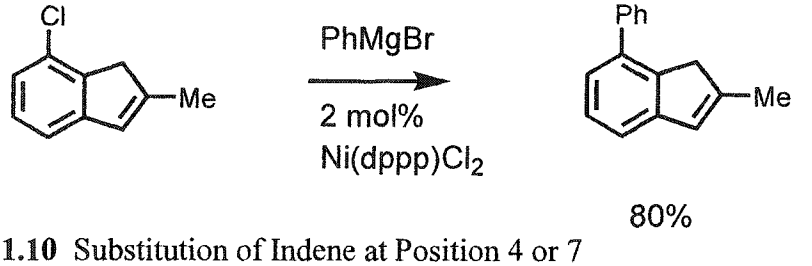
cross-coupling reaction usually allows for successful optimization. Ivchenko *et. al.*, in a recent advancement of this technique, expanded the scope of this cross-coupling reaction by introducing 3-alkyl-2-bromoindenes and successfully



Scheme 1.9 Substitution of Indene at Position 2

demonstrating that even the hindered 3-*t*-butyl –2-bromoindene would couple with methyl magnesium iodide in the presence of nickel catalyst (Scheme 1.9) [17].

This palladium or nickel catalyzed cross-coupling reaction may be used to synthesize indenes substituted in the 4 and 7 positions from 7-chloroindenes or 7-bromoindenes (Scheme 1.10). Unfortunately, the synthesis of these starting materials may be lengthy [18].



Scheme 1.10 Substitution of Indene at Position 4 or 7

Indenes with substituents in the 4 and 7 positions (Figure 1.6) may also be synthesized through a 1,4-diketone and cyclopentadienyl anion condensation, which works well for primary and aryl substituents and moderately well for the incorporation of a single *iso*-propyl group, although not at all for incorporation of a single *tert*-butyl group [8,19].

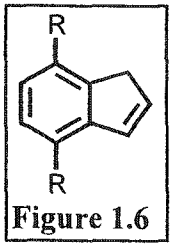


Figure 1.6

Addition to indanones followed by dehydration may be used to regioselectively obtain indenes substituted in the 1 and 2 positions

(Figure 1.7) [8]. The addition of Grignard reagents to indan-1-one works well for primary alkyl groups, but results in low yields for secondary alkyl groups . The addition of primary and aryl Grignard reagents to indan-2-one proceeds with moderate yields. The yields of these approaches may suffer when deprotonation of the indanones to form enolates occurs rather than addition.

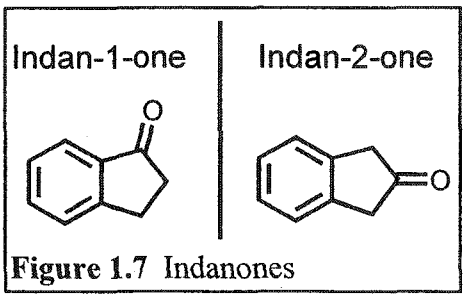
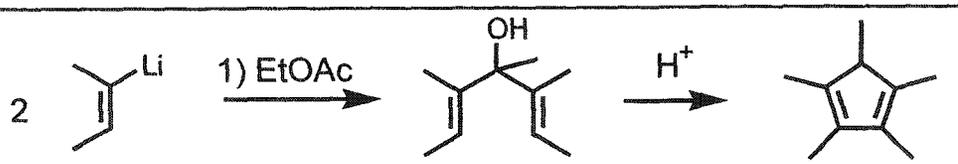


Figure 1.7 Indanones

There are several good regioselective methods involving the derivatization of existing five-membered rings for the regioselective synthesis of substituted indenes. These include direct alkylation, nickel and palladium catalyzed cross-coupling reactions, condensation of 1,4 diketones with cyclopentadienyl anion, and addition to or reduction of indanones. Difficulties may be encountered with all of these methods when indenes with bulky alkyl substituents are being synthesized.

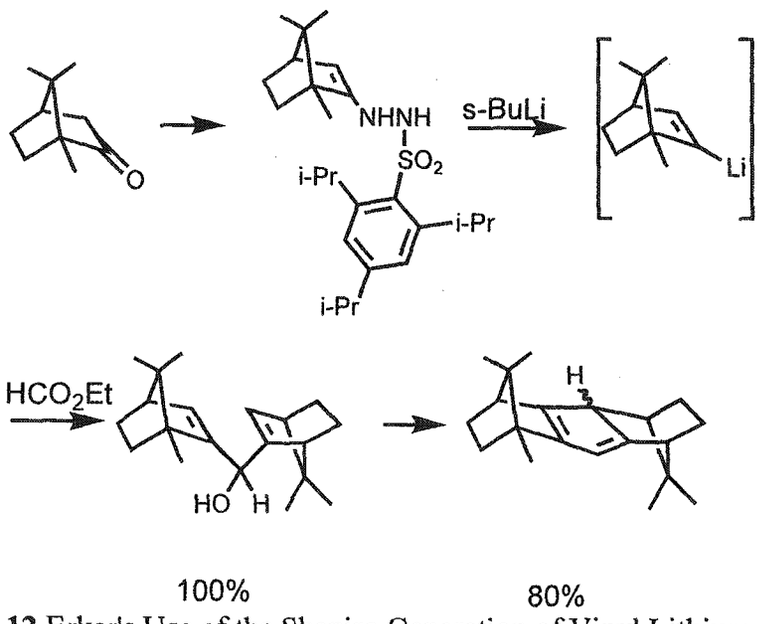
1.2.3 Cyclopentadienes: Five-Membered Ring Forming Methodologies

Some methods for synthesis of substituted cyclopentadienes through the formation of five-membered rings include: cationic 4π electron electrocyclic ring closures, the Skattebol carbene rearrangement, and a variety of methods to form cyclopentenones such as the Wittig method, the Noyori annelation, and the Pauson-Khand reaction, in addition to formation of cyclopentadienones with a bis-aldol condensation.



Scheme 1.11 Bercaw's Method of Cyclopentadiene Synthesis

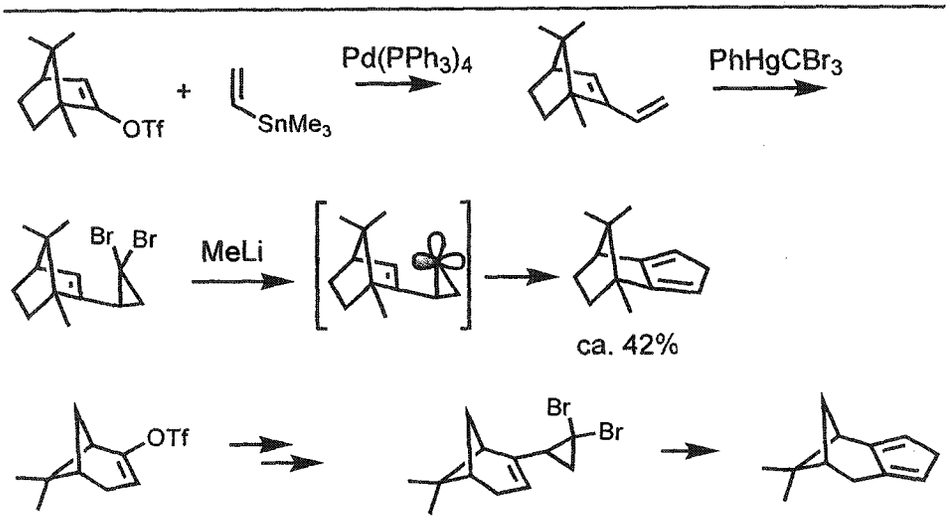
Paramount among five-membered ring forming methodologies for cyclopentadiene synthesis are cationic 4π electron electrocyclic ring closures, commonly known as Nazarov cyclizations. Bercaw developed the most applied variation in 1977, as a 2-step synthesis of pentamethyl cyclopentadiene (Scheme 1.11) [20]. The one-step synthesis of bis-allylic alcohols needed for Bercaw's



Scheme 1.12 Erker's Use of the Shapiro Generation of Vinyl Lithium

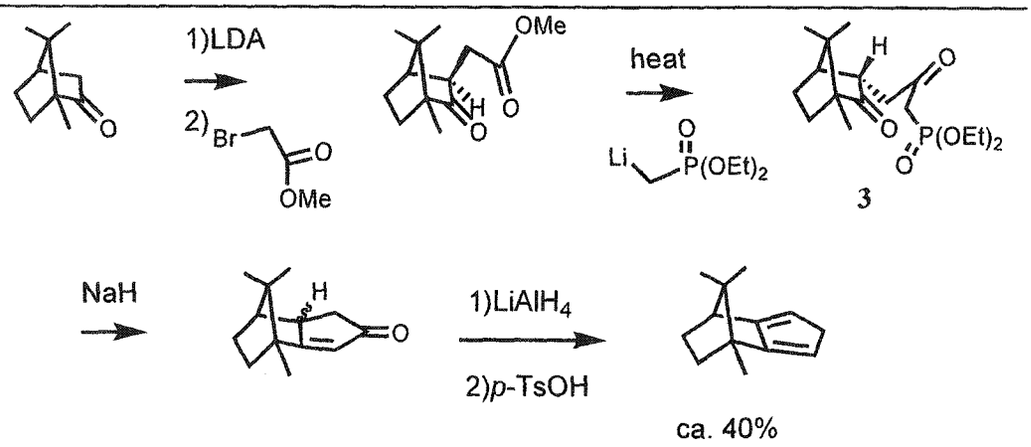
method may be problematic [21]. However, a more reliable route, using the Shapiro reaction to generate the lithium reagent, has been developed by Erker and was used to make several very hindered chiral cyclopentadienes from camphor and β-pinene (Scheme1.12) [5,22].

Over the years, there have been many other methods used to synthesize chiral annelated cyclopentadienes from camphor and β-pinene



Scheme 1.13 Cyclopentadienes via the Skattebøl Rearrangement

(nopinone may be easily obtained from β-pinene by ozonolysis). Paquette's four-step synthesis of camphor and β-pinene-annelated cyclopentadienes via the Skattebøl reaction of dibromo-derived carbenes (Scheme 1.13) is perhaps the most intriguing [23]. However, the use of organotin and organomercury reagents limits the appeal of this method and, in some cases, the Skattebøl rearrangement results in an allene side product that decreases the yield significantly.



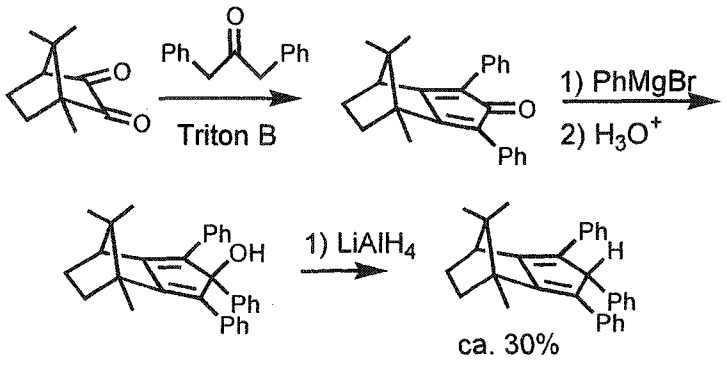
Scheme 1.14 Chiral Cyclopentadiene via the Wittig Method

Since expensive reagents made this method completely impractical for larger scales, Paquette applied a cheaper Wittig method that had been

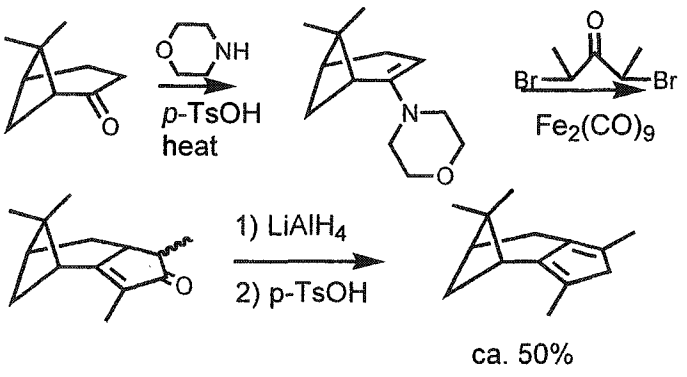
introduced by Halterman and Vollhardt, and improved the synthesis of the diketo phosphonate precurser **3** (Scheme 1.14) [24].

Clearly, the allure of obtaining chiral cyclopentadienes by annelation with these readily available chiral molecules remains a wonderful incentive for development of new synthetic methodology. Other well-established methods have been used to approach similar ligands including bis-aldol condensation to make cyclopentadienones (Scheme 1.15a), and Noyori annelations (Scheme 1.15b) or Pauson-Khand reactions (Scheme 1.15c) to make cyclopentenones; both may be converted to cyclopentadienes [25].

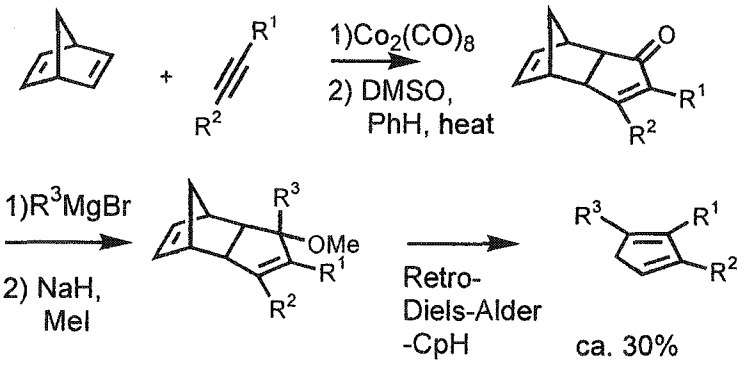
a) Bis-Aldol Cyclopentadienone Formation Followed by Addition and Reduction



b) Noyori Annelation to Cyclopentenone Followed by Reduction and Dehydration

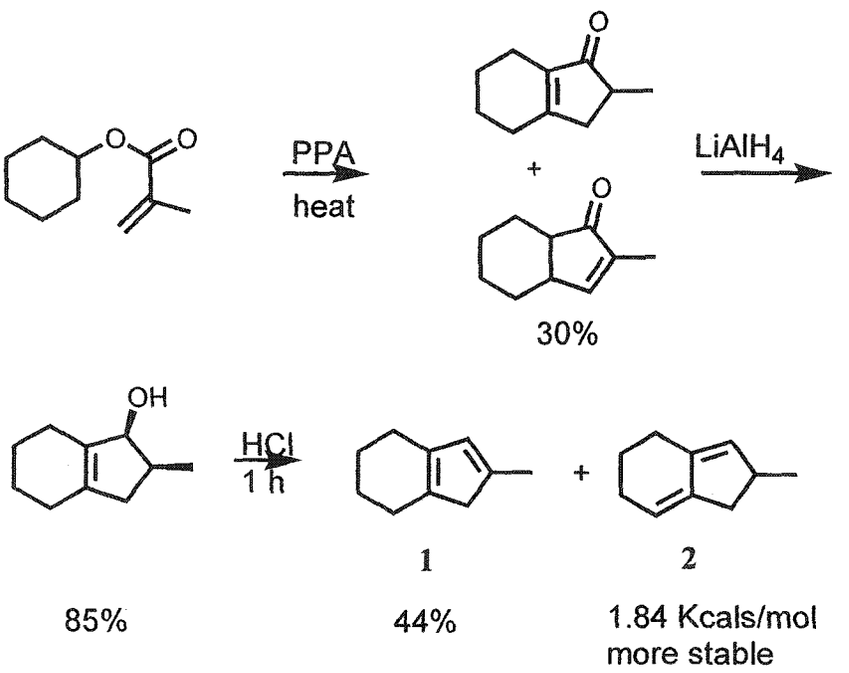


c) Pauson-Khand Cyclopentenone Formation Followed by Addition and Elimination



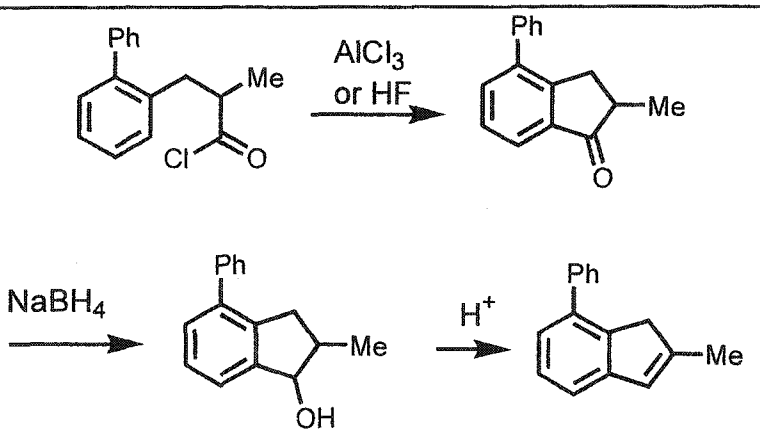
Scheme 1.15 Substituted Cyclopentadienes by Annelation Methods

In a substituted tetrahydroindene synthesis, a Nazarov cyclization was used to make the substituted cyclopentenone (Scheme 1.16) [13]. The cyclization proceeded with a moderate yield of 30%. However, as previously mentioned, the tetrahydroindene rearranged under the acidic conditions used for dehydration after reduction, which constituted a major problem with this method.



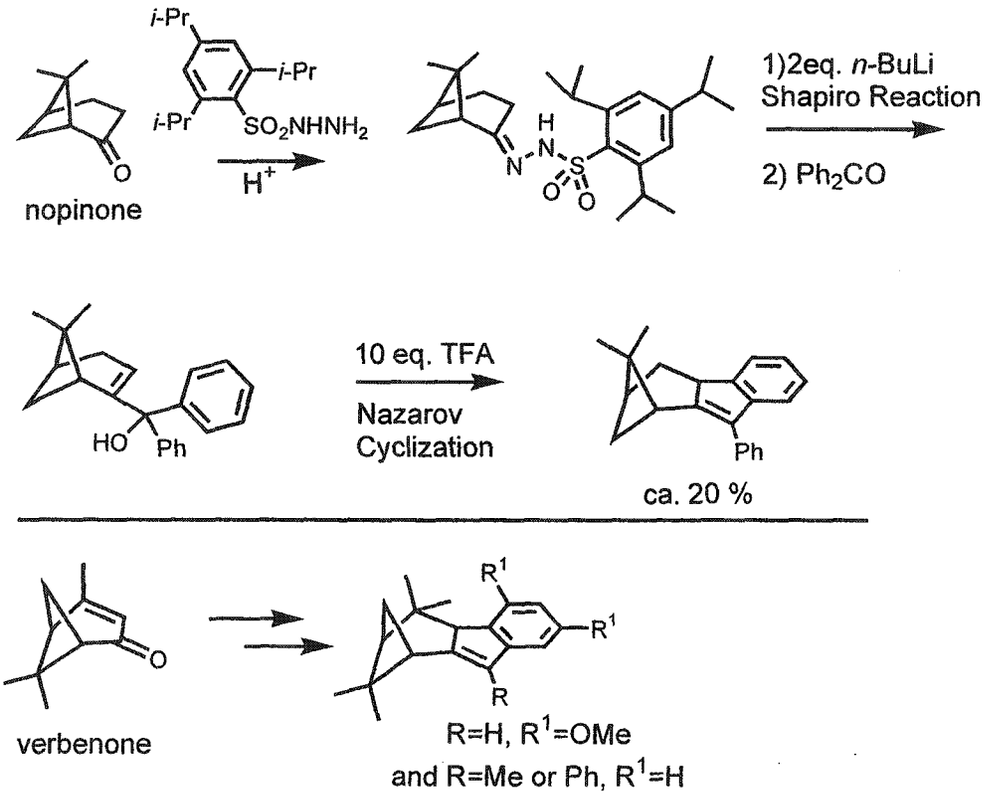
Scheme 1.16 Tetrahydroindene from Nazarov Cyclization to Cyclopentenones

1.2.4 Indenes: Five-Membered Ring Forming Methodologies



Scheme 1.17 Indene from an Intramolecular Friedel-Crafts Reaction to Indanone

Indenes may also be synthesized by annelation methods that form five-membered rings. The methods most commonly used involve Friedel-Crafts reactions and Nazarov-type cyclizations [26]. These rather harsh methods may require significant effort to optimize conditions, with different acid catalysts being explored before a satisfactory procedure is found. However, they are attractive methods for large scale application and the incorporation of substituted benzenes (e.g. alkylbenzenes, halobenzenes) into the syntheses allows for various substituents of steric and electronic interest to be incorporated with the six-membered ring onto the indenes (Scheme 1.17) [4]. Unfortunately, in some cases, numerous steps may be involved in preparing the Friedel-Crafts substrate from readily available materials. Using the Nazarov cyclization method several chiral annelated indenes have been synthesized from nopinone and verbenone (Scheme 1.18) [27].



Scheme 1.18 Chiral Indenes through Nazarov Cyclization

In this overview of synthetic methods, we have seen that while a variety of methods exist for the synthesis of cyclopentadienes, tetrahydroindenes, and indenes, there are some repeated difficulties which might be overcome with the development of new synthetic methodologies. For cyclopentadienes, the milder methods are not generally regioselective. For tetrahydroindene, acid catalyzed rearrangement to more stable s-*trans* diene isomers may lower the yields. While for indenes, methods with milder conditions than the Nazarov and Friedel-Crafts cyclizations are needed.

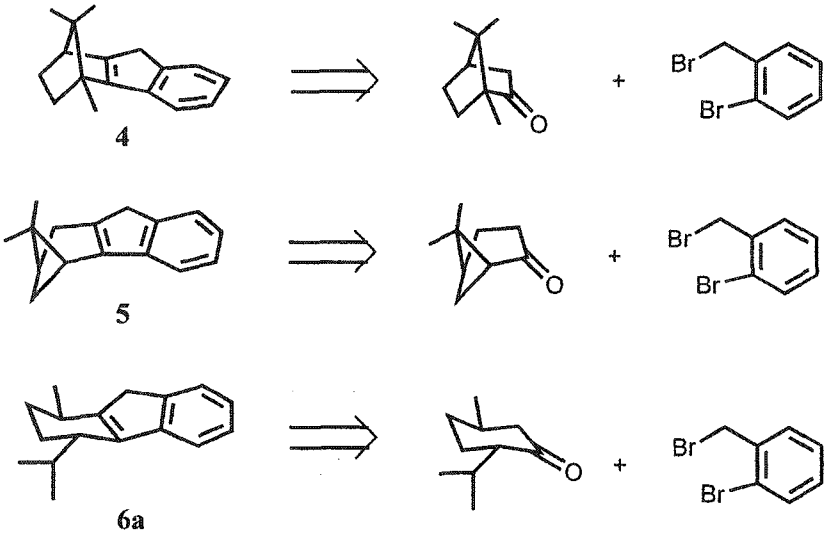
Chapter 2

Novel Carbonyl Addition Method

2.1 Development of a New [3+2] Methodology by Halterman and Zhu

Although there exist many methods for the formation of cyclopentadiene ligands from the diverse collection of readily available chiral ketones, there are only a few methods for the formation of annelated indene ligands such as those shown in Scheme 2.1 from these attractive substrates. The new carbonyl addition [3+2] methodology described here was developed by

[2+3] Strategy for Five-membered Ring Formation



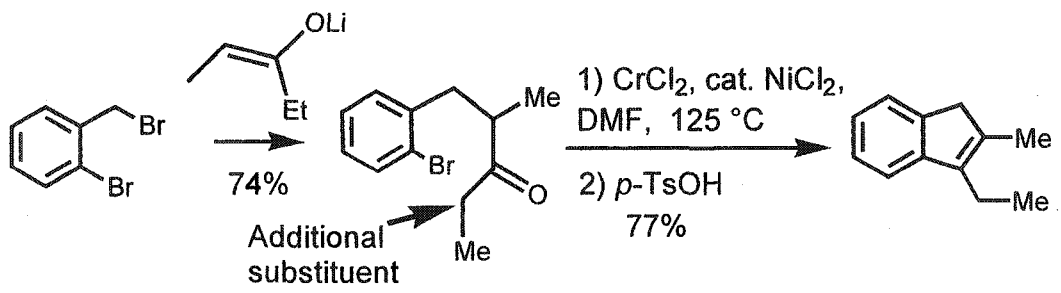
4 5 6a

Scheme 2.1 Retrosynthetic Approach to Chiral Indenes

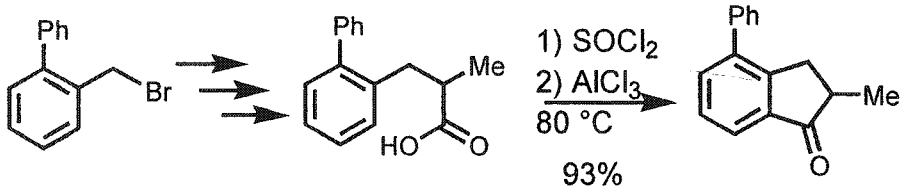
Halterman and Zhu and serves as one of the few alternatives to the Nazarov and Friedel-Crafts cyclization methods discussed earlier. The intent behind the development of this new methodology was to provide a regioselective method that used milder conditions to achieve ring-closure than the two classic acid catalyzed cyclization methods. After providing some background, we will describe our own application of this method to the synthesis of the chiral indenes in Scheme 2.1, and our attempt to extend the method to the synthesis of cyclopentadienes and tetrahydroindenes.

The novel three-step ring-forming methodology that Halterman and Zhu developed as a milder alternative for the synthesis of indenes involves enolate alkylation and intramolecular carbonyl addition via the Nozaki-Hiyama-Kishi coupling reaction, followed by dehydration [28]. This new method shares certain efficiencies with the Nazarov cyclization method that are lacking in the Friedel-Crafts method, in particular there is an efficiency of steps that results from the cyclization product being either an indene or indanol with additional substituents already incorporated, rather than an indanone which must be converted to an indene through reduction, or addition, followed by dehydration (Scheme 2.2).

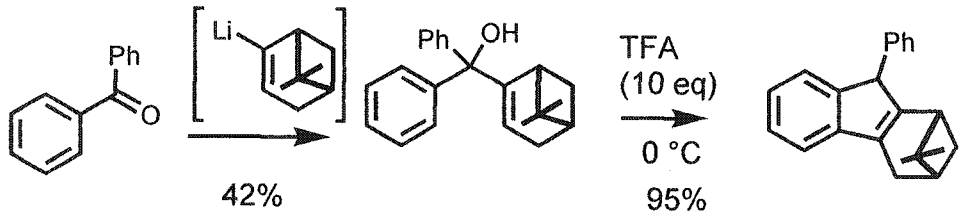
Halterman and Zhu Carbonyl Addition [3+2] Ring-Closing Methodology



Friedel-Crafts [3+2] Ring-Closing Methodology

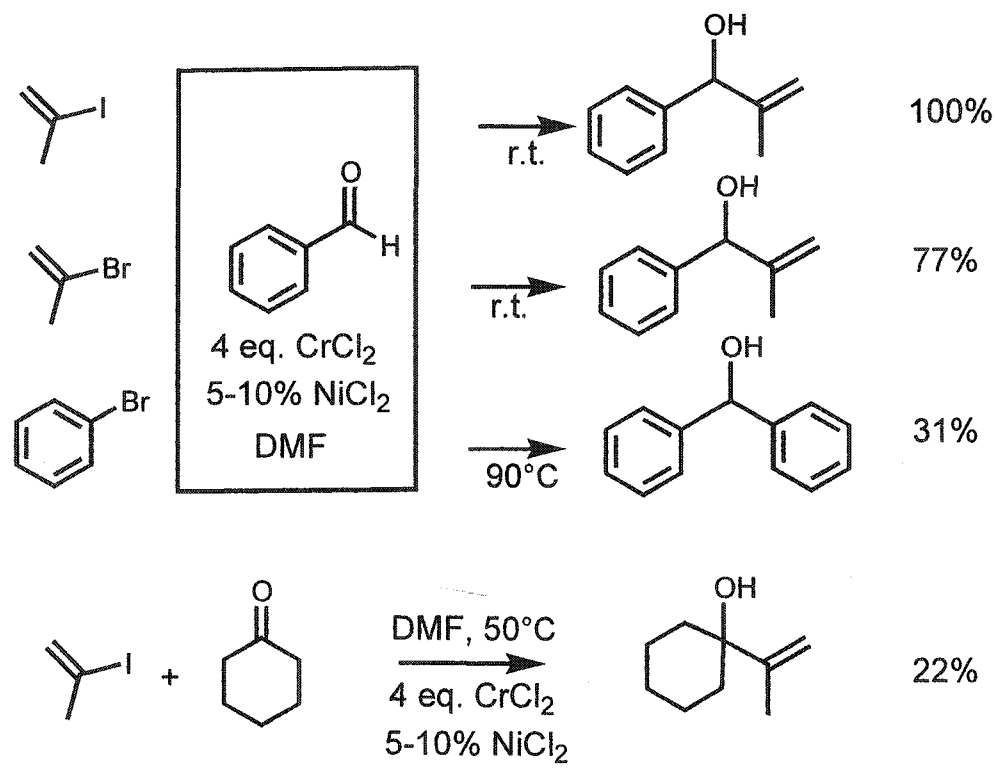


Nazarov [3+2] Ring-Closing Methodology



Scheme 2.2 [3+2] Ring-Forming Methodologies for Indene Synthesis

For the intramolecular carbonyl addition step, which is the centerpiece of this methodology, Halterman and Zhu turned to a coupling reaction that has gained a reputation in natural products synthesis as a mild method for adding vinyl halides to aldehydes and is known as the Nozaki-Hiyama-Kishi or Ni(II)/Cr(II)-mediated coupling reaction [29]. At the time, this reaction was only known to give excellent or quantitative yields for the coupling of vinyl iodides and vinyl bromides with aldehydes (Scheme 2.3)[30]. The mechanism of this addition may proceed through activation of the vinyl halide bond with nickel (0) or nickel

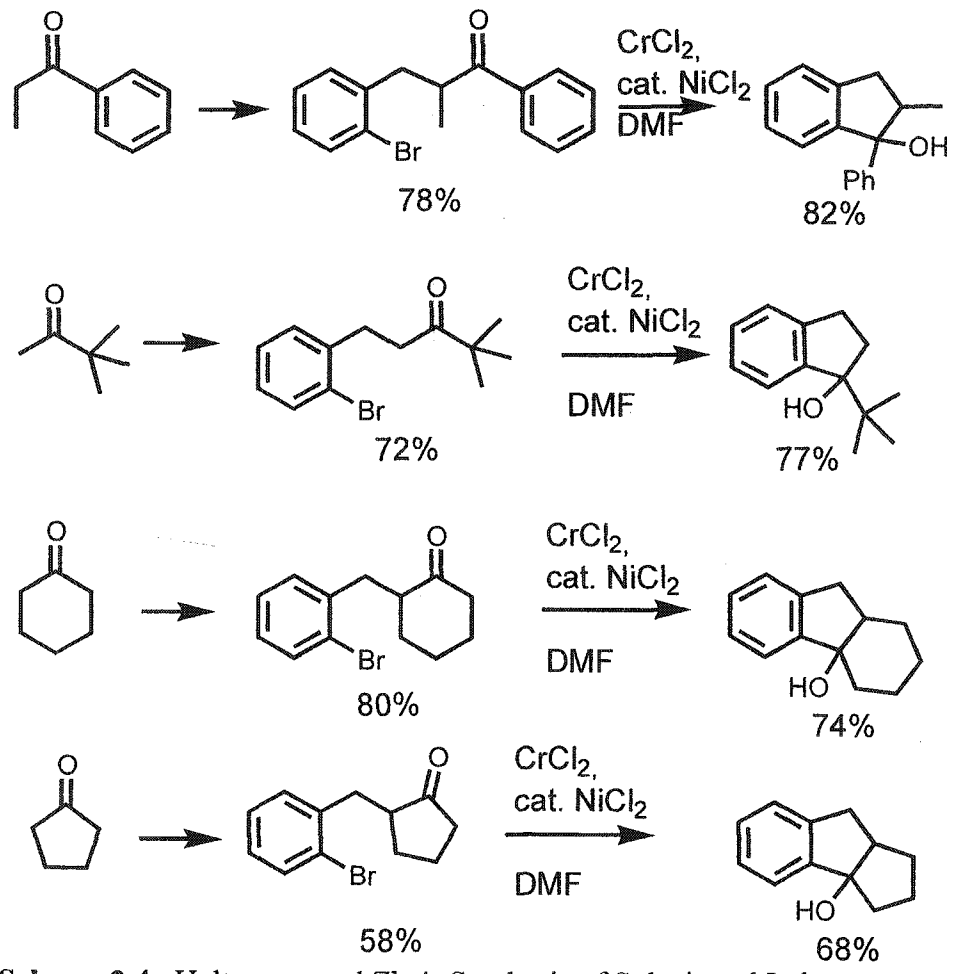


Scheme 2.3 Scope of the Nozaki-Hiyama-Kishi Coupling Reaction

(I) and transmetalation to form a vinylic chromium (III) dichloride complex, which undergoes addition to the carbonyl moiety [31]. In practice, an excess of greater than two equivalents of chromium (II) chloride, a single electron donor, is needed for the reaction. Later, we will discuss the newer catalytic conditions developed by Fürstner and Shi, which are stoichiometric in manganese (0) and catalytic in chromium (II) chloride [32].

In order to apply this reaction to the synthesis of substituted indenes, Halterman and Zhu extended the scope of this reaction to the intramolecular coupling of aryl bromides with ketones rather than aldehydes [28]. This modification required higher temperatures around 125 °C, but gave good coupling yields (77-82%) with acyclic ketones (Scheme 2.4). Moderate yields (45-74%)

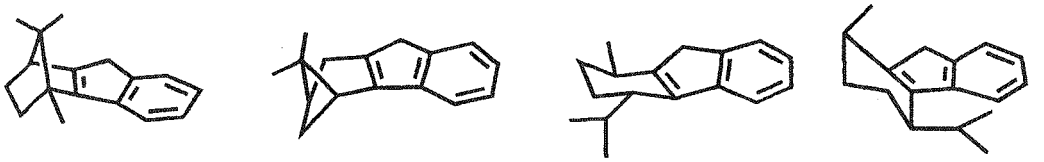
Alkylation and Carbonyl-Addition to form Indanols



Scheme 2.4 Halterman and Zhu's Synthesis of Substituted Indenes

were obtained for annelations to ketones with five and six-membered rings, such as would be necessary for the synthesis of indenes from chiral ketones such as camphor, menthone, and nopinone. This new three-step method of alkylation, carbonyl addition, and dehydration gave overall yields for mono- and disubstituted indenes that ranged from 29-58%.

2.2 Synthesis of Chiral Indenes with the New Carbonyl Addition Method

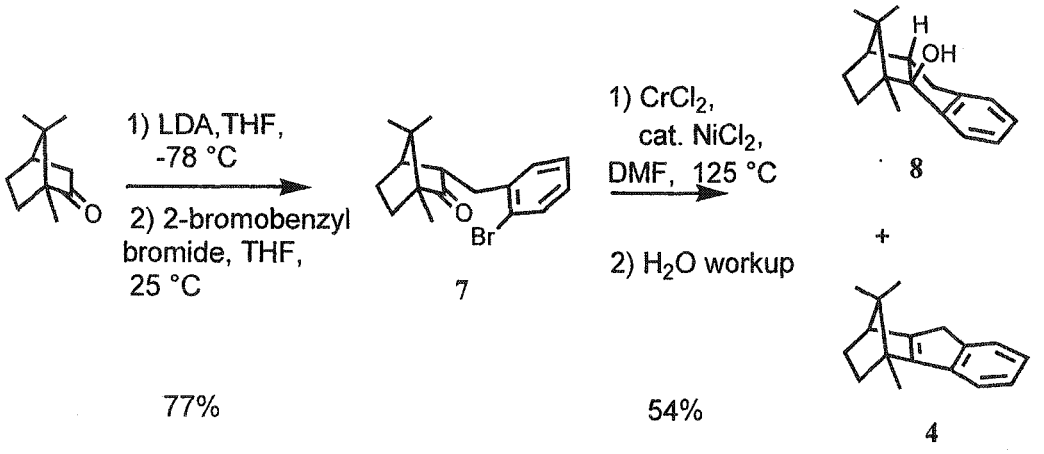


4 **5** **6a** **6b**

Figure 2.1 Chiral Indenes Synthesized with Carbonyl Addition Methodology

With this novel methodology developed by Halterman and Zhu, we have proceeded to synthesize new chiral annelated ligands, **4-6,** from readily available chiral ketones: (1*R*)-(+)-camphor, (1*R*,5*S*)-(+)-nopinone, and (-)-menthone [33].

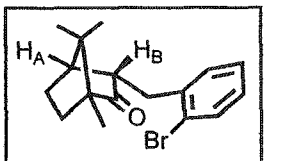
2.2.1 The Synthesis of a Camphor Annelated Indene



Scheme 2.5 Alkylation of Camphor and the Carbonyl Addition Reaction

In the synthesis of the (1R)-(+)-camphor annelated indene **4**, good regioselectivity for C-alkylation was achieved by alkylation at room temperature,

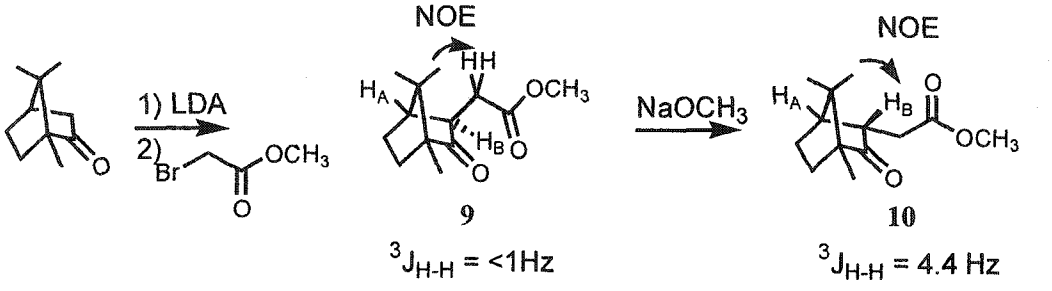
with 1.5 eq. 2-bromobenzyl bromide, of the lithium enolate of camphor, which was generated at -78 °C. The tethered ketone **7** was isolated as a yellow oil in 77% yield after filteration to remove camphor and removal of the excess 2-bromobenzyl bromide by vacuum distillation. An 83:17 ratio of the endo and exo isomers of tethered ketone **7** was observed in the ^{1}H-NMR spectrum. The coupling constant of 4.0 Hz between the bridgehead proton (H_A) and the proton alpha to the ketone (H_B) observed for the major isomer seems most consistent with the structure shown in Figure 2.2, when compared to the reported coupling



7

J_{A-B} = 4.0 Hz

Figure 2.2

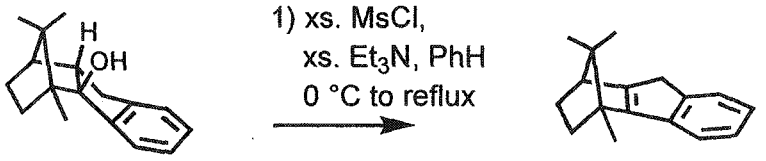


9 **10**

$^3J_{H-H}$ = <1Hz $^3J_{H-H}$ = 4.4 Hz

Scheme 2.6 Known Stereochemistry of Camphor Enolate Alkylation

constants of the analogous alkylated camphor isomers shown in Scheme 2.6, for which NOE experiments were used to assign the stereochemistry [34]. Efficient cyclization of ketone **7** with 3.0 equivalents of $CrCl_2$ and 5 mol% $NiCl_2$ in DMF at 125 °C overnight gave the alcohol **8**, presumably of the indicated stereochemistry, in 49% yield after isolation by column chromatography and some small amount (5%) of the indene **4** from dehydration *in situ*.



Scheme 2.7 Dehydration to the Camphor Annelated Indene

Dehydration of the alcohol with *p*-toluenesulfonic acid in refluxing benzene was abandoned due to some difficulties with cationic decomposition of the bicyclic structure, which led at least in part to cleavage of the one carbon bridge to form what by initial inspection of spectral data looked to be a menthyl skeleton. Instead, a base-promoted elimination procedure was employed. Methanesulfonyl chloride (1.5 eq.) was added at 0 °C to the annelated indanol **8** in benzene and excess triethylamine, then the mixture was refluxed for 16 hours. After being cooled again to 0 °C, additional methanesulfonyl chloride (0.75 eq.) was added and refluxing was continued for an additional 16 hours. This procedure resulted in complete conversion of the alcohol **8** to the indene **4**, which was isolated as a pure brown oil in 100% yield after extraction. This synthesis reliably gave the camphor annelated indene **4** in an overall yield of 42% in 3 steps.

The ^{1}H-NMR, ^{13}C-NMR, DEPT, and low resolution mass spectral data for the final product were all consistent with the structure of the camphor annelated indene **4**. The low resolution mass of 224 (90 rel%) and several diagnostic NMR spectral signals allowed us to confidently identify the structure of the indene. The bis-allylic geminal protons were observed in the ^{1}H-NMR spectrum as doublets at 3.31 and 3.07 ppm that coupled each other with the expected large 23 Hz geminal

coupling constant. Three methyl singlets were observed, one of which, at 1.39 ppm (20.5 ppm in the ^{13}C-NMR spectrum), was significantly deshielded in comparison to the other two at 0.87 and 0.83 ppm (19.8 and 12.5 ppm in the ^{13}C-NMR spectrum). This deshielding effect is an interesting contrast to the shielding effect observed in the camphor annelated cyclopentadiene (Figure 2.3) [34]. We are not certain whether the deshielded methyl signal of this indene corresponds to the analogous but shielded methyl group of the cyclopentadiene or to the bridgehead methyl situated in the "bay area" of the indene structure proximate to the deshielding zone of the benzene ring (Figure 2.3).

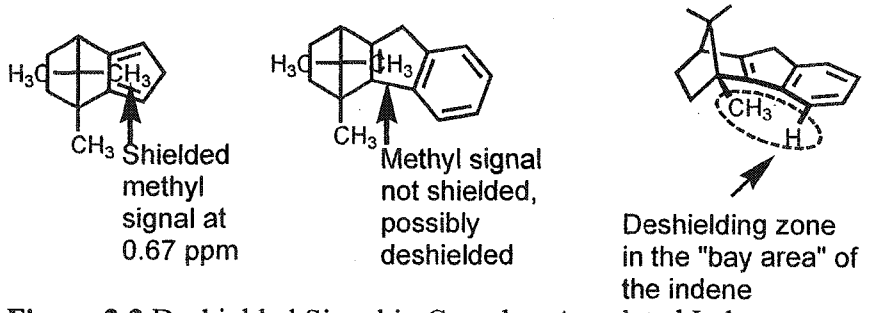
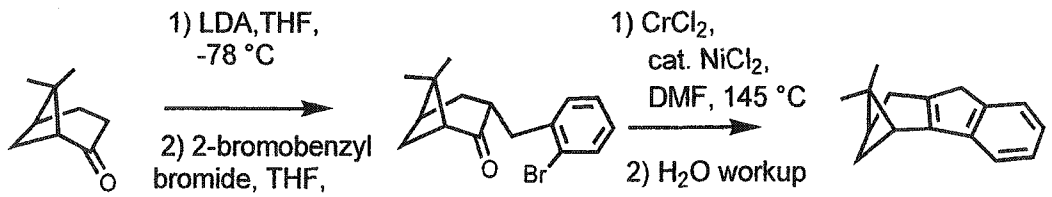


Figure 2.3 Deshielded Signal in Camphor Annelated Indene

2.2.2 The Synthesis of a Pinanyl Annelated Indene

Not only was the chiral indene synthesis successful with camphor, but we also were able to convert nopinone to indene **5**. Alkylation of the lithium enolate of (1R,5S)-(+)-nopinone generated at -78 °C with 2-bromobenzyl bromide at room temperature proceeded regio- and stereoselectively with moderate to good yields (Scheme 2.8). The tethered ketone **11** was purified as a white solid (mp 117-120 °C) by recrystallization from hexanes. The stereochemistry portrayed is consistent



Scheme 2.8 Synthesis of a Pinanyl Annelated Indene

with the reported kinetic diastereoselectivity under these alkylation conditions for other electrophiles [35]. The coupling of ketone **11** using 3.0 equivalents of $CrCl_2$ and 5 mol% $NiCl_2$ in DMF would only proceed at elevated temperatures (145 °C) over a prolonged time period of 80 hours; consequently, the dehydrated product was isolated upon aqueous workup. Unfortunately, the yield of this coupling reaction (39%) was dramatically reduced by the formation of a dimeric side product, which in the best instance cut the yield by 12%. The dimeric side product was determined by mass spectrometry (EI, 70 eV) to have a molecular mass of 456. This mass would be consistent with the intermolecular coupling of two molecules of the tethered ketone resulting in the formation of a ten membered ring with two alcohols. As might be expected if this were the case, this side product was easily separated from the nopinanyl indene **5** by column chromatography, which allowed isolation of indene **5** in 39% yield as a yellow oil.

The ^{1}H-NMR, ^{13}C-NMR, DEPT, and low resolution mass spectral data for the final product were all consistent with the structure of the pinanyl annelated indene **5**. A low resolution mass of 210 (100 rel%) was obtained. The characteristic bis-allylic geminal protons for this indene were seen at 3.29 ppm and 3.24 ppm with the typically large coupling constant of 23 Hz. The two

singlets of the methyl group protons were observed at 1.42 ppm and 0.72 ppm in the ^{1}H-NMR spectrum (26.8 ppm and 21.6 ppm in the ^{13}C-NMR spectrum). The downfield signal probably corresponds to the methyl group proximate to the indenyl ring system, since this methyl group may be situated in a deshielding zone (Figure 2.4). Likewise, on the opposite side of the indenyl system, the same pattern of deshielding is observed for the geminal protons of the one carbon bridge. One proton signal is markedly downfield at 2.61 ppm compared to the other at 1.33 ppm (Figure 2.4).

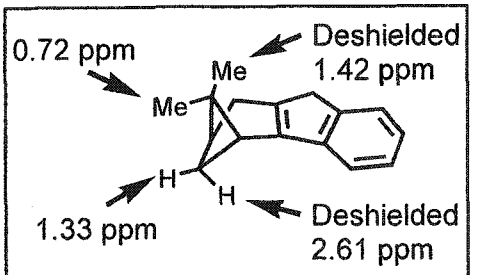
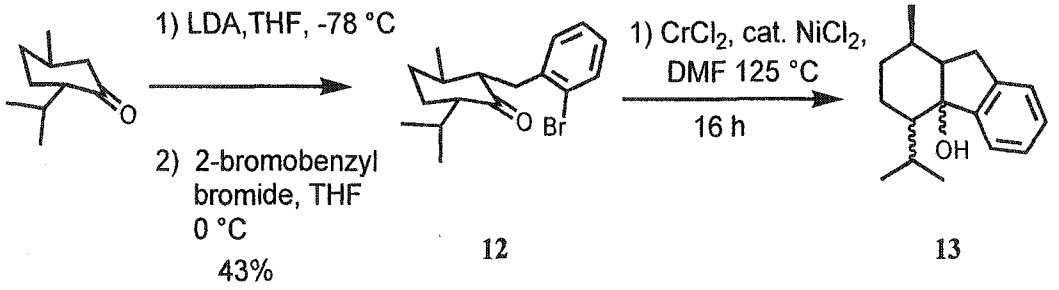


Figure 2.4 Deshielded Signals in Pinanyl Annelated Indene

2.2.3 The Synthesis of a Menthyl Annelated Indene



Scheme 2.9 Alkylation of Menthone Enolate and Carbonyl Addition

We also examined the use of (-)-menthone as a chiral starting material for indene synthesis with this methodology. The alkylation of the enolate of (-)-menthone generated at -78 °C with 2-bromobenzylbromide was performed at 0°C (Scheme 2.9). The isolated yields of a single tethered ketone isomer **12**, a colorless oil, by column chromatography were only moderate. NMR spectroscopic and X-ray crystallographic studies in the literature of similar

reactions involving the irreversible generation of the enolate of (-)-menthone demonstrated that in the major product the isopropyl group had not epimerized, even though this epimerization frequently occurs in basic as well as acidic media [36].

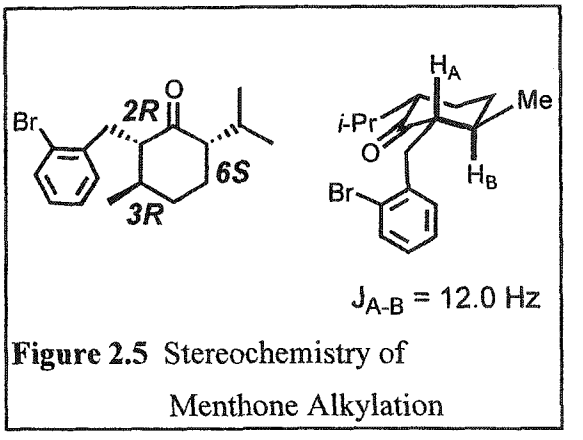
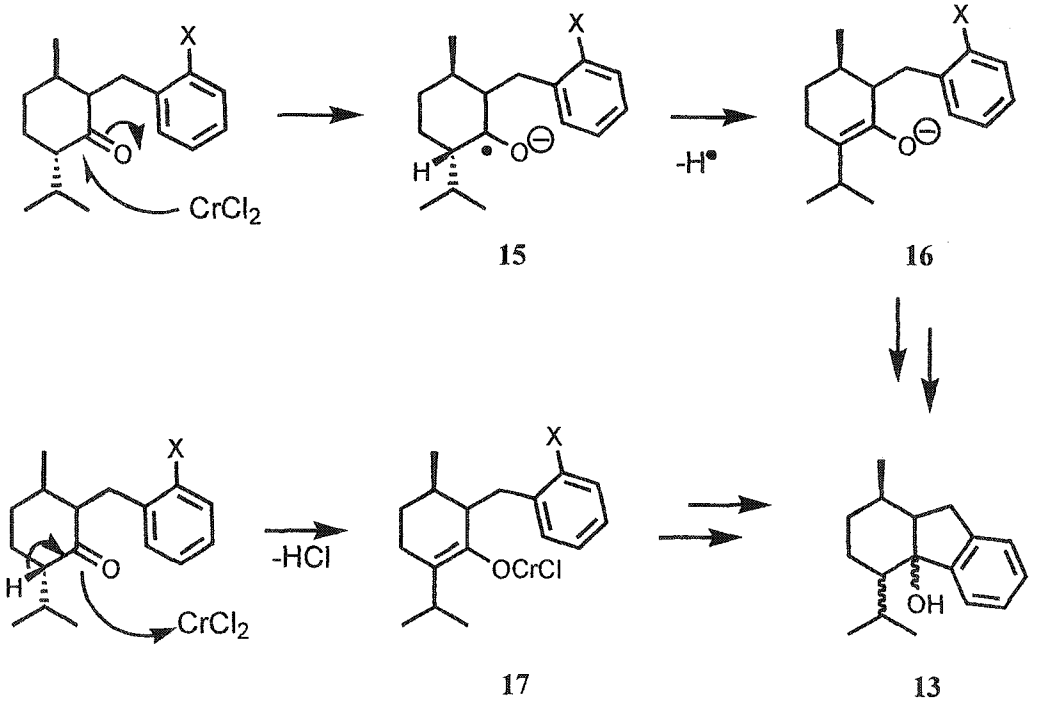


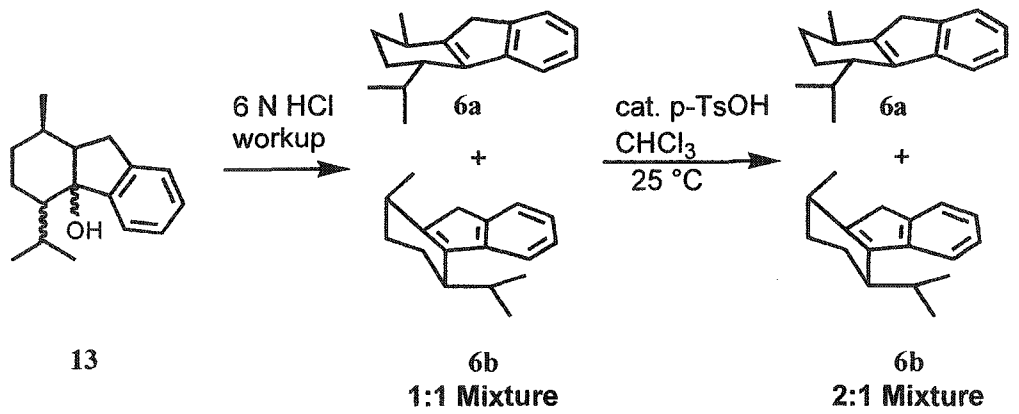
Figure 2.5 Stereochemistry of Menthone Alkylation

The characterization by ^{1}H-NMR spectroscopy of the tethered ketone **12** seems consistent with the *2R, 3R*-isomer shown because of the observed axial-axial coupling constant of 12.0 Hz for the two *trans*-diaxial vicinal protons shown as H_A and H_B in Figure 2.5 [36].

The coupling of ketone **12** proceeded well with 3.0 equivalents of $CrCl_2$ and 5 mol% $NiCl_2$ in DMF at 125 °C overnight, however, following a simple

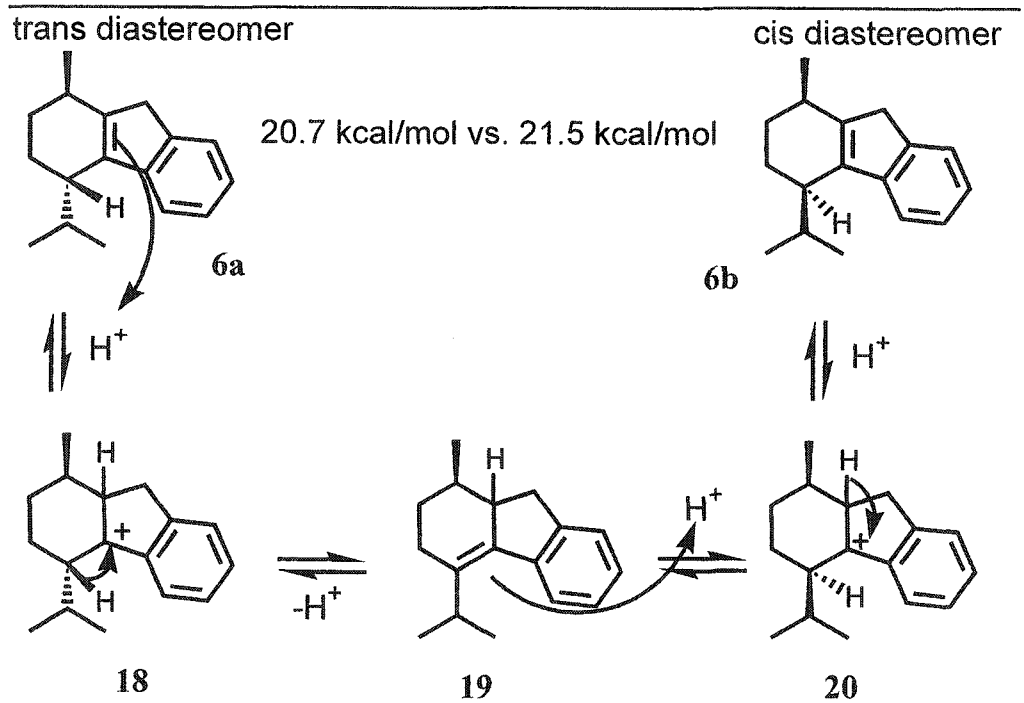


Scheme 2.10 Menthone Carbonyl Addition: Possible Epimerization Pathways



Scheme 2.11 Dehydration to and Isomerization of Menthyl Annelated Indenes

aqueous workup, numerous isomers of the annelated indanol **13** were isolated. This complex mixture of alcohol isomers **13** apparently resulted from epimerization of the isopropyl group due to either the strongly reducing or the Lewis acidic nature of the coupling conditions (Scheme 2.10). When a 6N HCl workup was used to dehydrate the alcohols, a 1:1 mixture of the *cis* and *trans* menthyl annelated indene isomers **6a** and **6b** was isolated as a colorless oil



Scheme 2.12 Acid Catalyzed Isomerization of Menthyl Indenes

(Scheme 2.11). After stirring in $CHCl_3$ with cat. TsOH at room temperature, the menthyl annulated indene mixture isomerized to an improved ratio of 2:1, which was evidence for an acid catalyzed epimerization mechanism for indenes **6a** and **6b** (Scheme 2.12). The isolated yield after coupling and dehydration was excellent (89%). However, the isomers **6a** and **6b** were not separable by chromatography. Consequently, attempts to determine whether the major component of the 2:1 mixture was the *cis* isomer **6b** or the *trans* isomer **6a** through COSY and NOESY experiments were inconclusive. However, AM1 calculations fixed the minimized *trans* isomer conformation at $\Delta H_f = 20.7$ kcal/mol, which was 0.8 kcals/mol more stable than the minimized *cis* isomer conformation at $\Delta H_f = 21.5$ kcals/mol. The characteristic bis-allylic geminal protons were observed for the major isomer at 3.35 ppm (J=3.0, 23.0 Hz) and 3.28 ppm (J=23.0 Hz) in the ^{1}H-NMR spectrum. The low resolution mass of 226 (100 rel%), and the ^{13}C-NMR and DEPT spectral data were all consistent with this isomeric mixture of indenes.

Thus, we found that this new carbonyl addition methodology, which Halterman and Zhu had demonstrated with the synthesis of 1,2 disubstituted indenes, could be applied to the synthesis of new annelated indenes from sterically hindered and strained bicyclic chiral ketones. In the case of the camphor annelated indene **4**, a reliable overall yield of 42% for three steps was observed. For the synthesis of the more strained nopinone derived indene **5**, where a higher temperature was required to force the carbonyl addition, our optimization efforts resulted in an overall yield of 26%, but much lower yields than 39% were frequently observed for the carbonyl addition step. In the synthesis of an

annelated indene from (-)-menthone, we discovered that while this new methodology may be milder than some of the classic methods for indene synthesis, the conditions are not mild enough to avoid the epimerization of a chiral center with an enolizable proton.

2.3 Attempted Syntheses of a Cyclopentadiene and a Tetrahydroindene with the New Carbonyl Addition Method

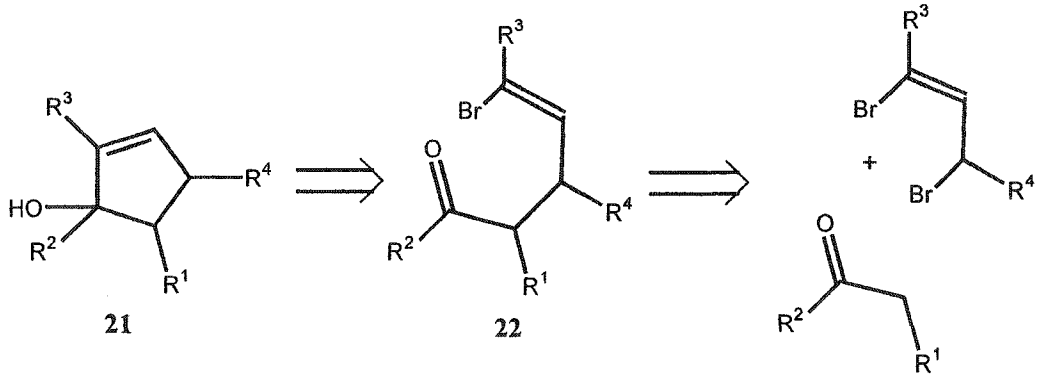
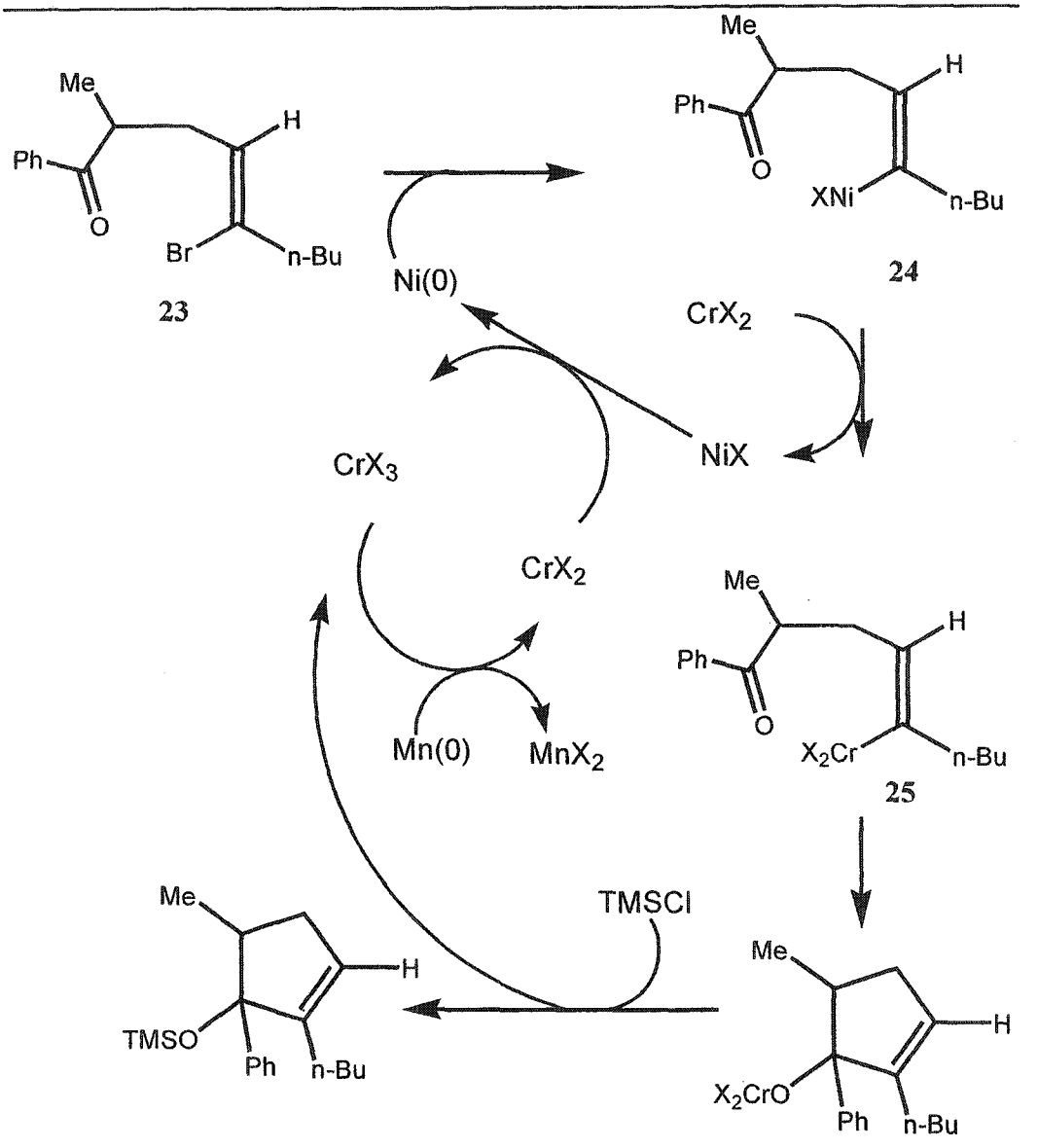
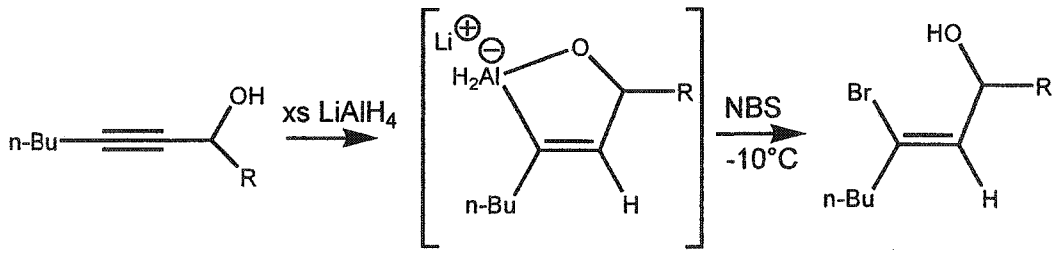


Figure 2.6 Retrosynthetic Scheme for Substituted Cyclopentadienes

We were interested in extending this method to regioselective syntheses of 1,2,3-tri- and possibly tetra-substituted cyclopentadienes (Figure 2.6) and this interest was encouraged by the development of a Nozaki-Hiyama-Kishi coupling protocol that is catalytic both in chromium (II) chloride and nickel (II) chloride through the introduction of stoichiometric quantities of manganese metal and chlorotrimethylsilane, an improvement which reduces both the expense and toxicity of the coupling reaction and makes it a far more attractive method for future use (Scheme 2.13)[32]. In this catalytic cycle developed by Fürstner, the Cr^{3+} generated by the coupling reaction is recycled to the necessary Cr^{2+} with the manganese metal as a stoichiometric reducing agent. The chlorotrimethylsilane is necessary for release of the Cr^{3+} from the alkoxide coupling product.



Scheme 2.13 Catalytic Cycle for the Nozaki-Hiyama-Kishi Reaction Using Manganese(0) as the Stoichiometric Reductant

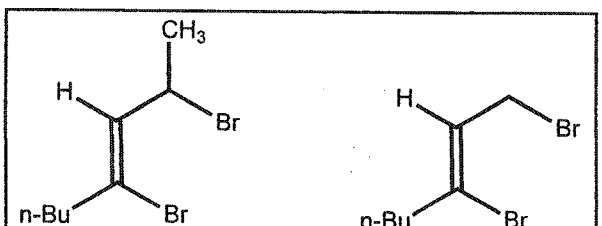


28 R=CH_3
29 R=H

60% yield **30** R=CH3
86% yield **31** R=H

Scheme 2.14 Regio- and Stereoselective Syntheses of (Z)-3-Bromoalk-2-en-1-ols

In order to achieve the synthesis of substituted cyclopentadienes via the Nozaki-Hiyama-Kishi coupling, we synthesized (Z)-2,4-dibromooct-3-ene **32** and (Z)-1,3-dibromohept-2-ene **33** for use as enolate alkylating agents (Figure 2.7). The appropriate alkynols **28** and **29** were easily obtained from 1-hexyne using methods found in the literature [37]. These propargyl alcohols were selectively transformed into (Z)-bromoalkenols **30** and **31** following the regioselective and stereoselective hydroalumination-bromination procedure of Garibyan and coworkers (Scheme 2.14) [38]. After using this method, which calls for quenching with a bromine-pyridine complex at -10 °C following reduction of the triple bond with lithium aluminum hydride, we chose to use anhydrous N-bromosuccimide in tetrahydrofuran at -10 °C to quench in order to avoid the inconvenience of forming the bromine-pyridine complex. However, if the



32 **33**

Figure 2.7 (Z)-Dibromoalkenes

temperature was any higher than 0 °C when the solvent is added to the N-bromosuccimide, a highly exothermic and hazardous process could occur, so this procedure must be used with caution. Starting material was generally recovered unless the propargyl alcohol was stirred at room temperature with 1.5 equivalents of lithium aluminum hydride over 72 hours. The use of 2 equivalents of N-bromosuccinimide to quench avoided the need to destroy any active lithium aluminum hydride with ethyl acetate. If moisture in the N-bromosuccinimide resulted in protonation of the vinyl anion instead of bromination, this side product was removed by vacuum. The isolated yields after extraction and column chromatography were usually good to excellent.

The characterization of these bromoalkenols by ^{1}H-NMR spectroscopy was consistent with the desired (*Z*)-bromoalkenol structure. For (*Z*)-3-bromohept-2-en-1-ol **31**, the observed ^{1}H-NMR spectral data in chloroform-d_1 solvent differed from the reported ^{1}H-NMR spectroscopic characterization of the undesired (*E*)-3-bromohept-2-en-1-ol, also in chloroform-d_1 solvent, both in chemical shift and coupling constant values (Figure 2.8) [39]. The low resolution mass spectral data for compound **31** contained the appropriate molecular mass isotope patterns and the base peak mass of 95 was consistent with fragmentation resulting in the loss of the hydroxyl group and bromine atom.

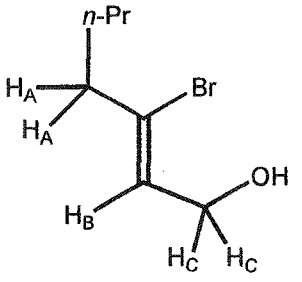
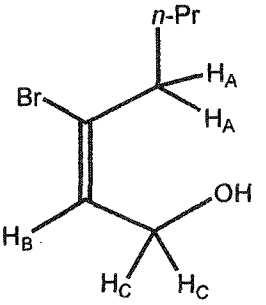
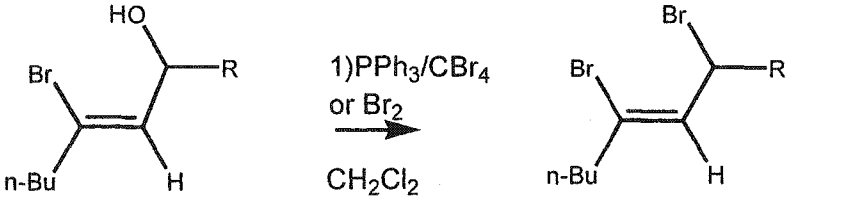
Desired Stereoisomer	Undesired Stereoisomer
(*Z*)-3-Bromohept-2-en-1-ol	(*E*)-3-Bromohept-2-en-1-ol
	
31	
Experimental Data in $CDCl_3$	Literature Data in $CDCl_3$
$\delta(H_A) = 2.41$ ppm	$\delta(H_A) = 2.50$ ppm
$\delta(H_B) = 5.88$ ppm	$\delta(H_B) = 6.11$ ppm
$\delta(H_C) = 4.22$ ppm	$\delta(H_C) = 4.11$ ppm
$J_{A\text{-}B} = 1.0$ Hz	
$J_{B\text{-}C} = 6.0$ Hz	$J_{B\text{-}C} = 8.0$ Hz
$J_{A\text{-}C} = 1.0$ Hz	

Figure 2.8 ^{1}H-NMR Spectroscopy Data Comparison

The resulting (Z)-bromoalkenols **30** and **31** were converted to (Z)-1,3-dibromoalkenes **32** and **33** by the slow addition of the (Z)-bromoalkenol at room temperature to a mixture of 2.8 equivalents of triphenylphosphine and 1.4 equivalents carbon tetrabromide (or bromine) in dichloromethane prepared at 0 °C. After 5 hours, filtration through silica gel and removal of impurities by extraction and trituration with petroleum ether, resulted in isolation of these (Z)-1,



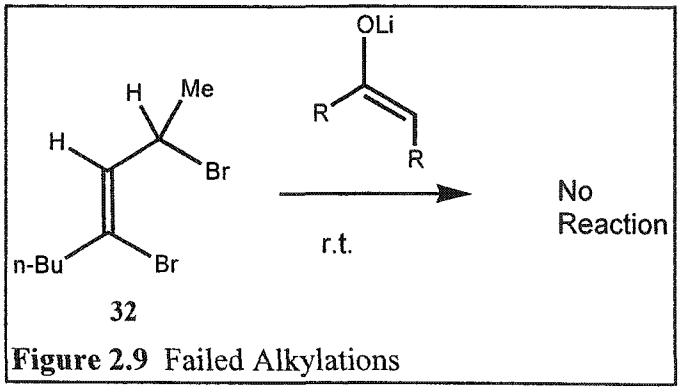
30 R=CH3
31 R=H

32 R=CH_3 85% yield
33 R=H 60% yield

Scheme 2.15 (*Z*)-1,3-Dibromoalkene Synthesis

3-dibromoalkenes **32** and **33** as colorless oils. This method was chosen and works well as a milder alternative to phosphorous tribromide procedures, which may cause cationic rearrangements. The signal for the brominated allylic methylene of (*Z*)-1,3-dibromohept-2-ene **33** was observed at 4.04 ppm in the ^{1}H-NMR spectrum and 41.3 ppm in the ^{13}C-NMR spectrum. Both values reflect an expected upfield shift when compared to the corresponding signals in the starting allylic alcohol **31** (4.22 ppm in ^{1}H-NMR spectrum and 62.3 ppm in the ^{13}C-NMR spectrum).

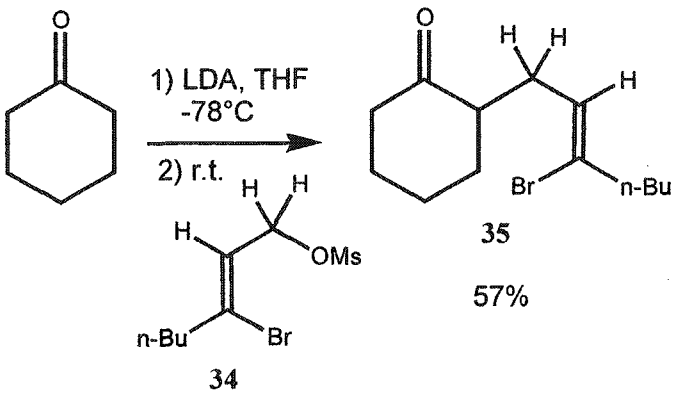
While the lithium enolates of a variety of ketones, including propiophenone, cyclohexanone, and pinacolone, alkylated readily with (Z)-1,3-dibromohept-2-ene **33**, we were disappointed to discover that the more hindered (Z)-2,4-dibromooct-3-ene **32** (see Figure 2.9) would not alkylate the enolates of acetophenone and cyclohexanone, even when more aggressive enamine alkylation methodology was employed. Due to this problem with the alkylation step, we were unable to extend the scope of this method to 1,2,3,4-tetrasubstituted cyclopentadienes.



32

Figure 2.9 Failed Alkylations

We considered synthesizing a monosubstituted 4,5,6,7-tetrahydroindene with this method, and were able to alkylate at room temperature the lithium enolate of cyclohexanone, generated at -78 °C, in an isolated yield of 57% using the mesylate of (Z)-3-bromohept-2-en-1-ol, compound **34** (Scheme 2.16). The low resolution mass of 273 (53 rel%) was consistent with the monoalkylated



Scheme 2.16 Alkylation of Cyclohexanone.

product **35** and the appropriate isotope patterns were observed. The compound was characterized by ^{1}H-NMR, ^{13}C-NMR, and DEPT spectroscopy. In the ^{1}H-NMR spectrum, the vinylic proton signal was split by two diastereotopic allylic protons (J=7.5 Hz and J=6.5 Hz) (Figure 2.10).

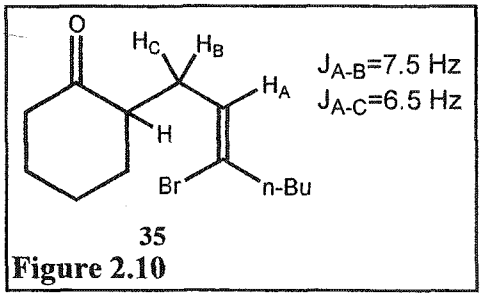


Figure 2.10

After the catalytic Nozaki-Hiyama-Kishi coupling reaction was run with this tethered ketone **35** at 125 °C using 10 mol% of chromium (II) chloride and nickel (II) chloride with 2 equivalents each of manganese (0) metal, chlorotrimethylsilane, and lithium bromide in dimethylformamide, recovered starting material and some other products were observed by ^{1}H-NMR spectroscopy. Upon careful consideration, it seemed probable that the Lewis acidic conditions of the coupling reaction might promote a double bond isomerization to a more stable s-*trans* bicyclo[4.3.0]nonadiene **38** (Figure 2.11) after the formation of the desired butyl substituted 4,5,6,7-tetrahydroindenes **36** and **37**, therefore we did not pursue the formation of isolable quantities of pure

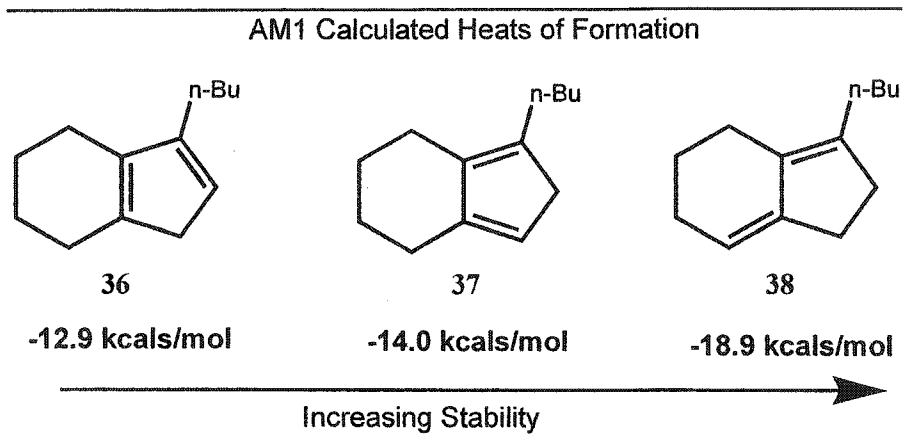
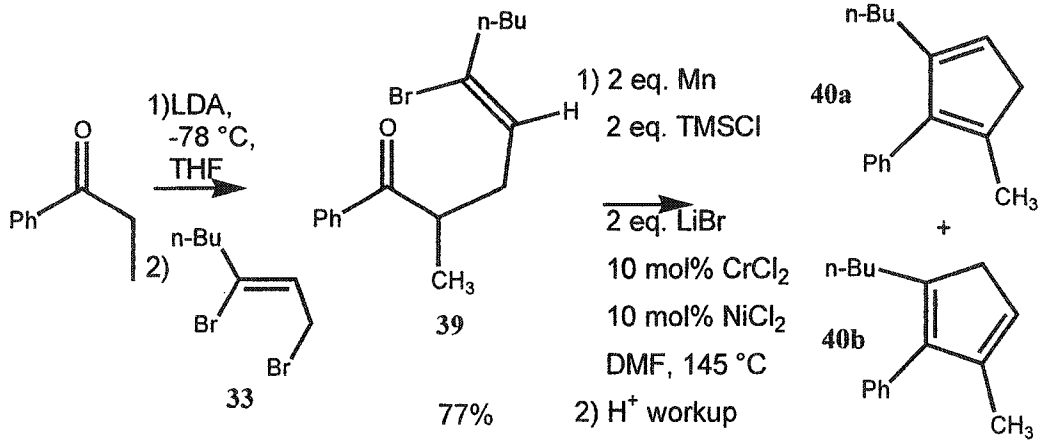


Figure 2.11 AM1 Calculated Tetrahydroindene Heats of Formation

products from this reaction.

Nonetheless, we continued our investigations into the scope of this method by undertaking the synthesis of the 1,2,3-trisubstituted cyclopentadiene isomers **40a** and **40b** shown in Scheme 2.17. The alkylation of the lithium enolate of propiophenone, generated at -78 °C, with (Z)-1,3-dibromohept-2-ene **33** at 0 °C proceeded with good yield (77%) and the tethered ketone **39** was readily isolated by column chromatography as a pale yellow oil (Scheme 2.17). The low resolution mass of 309 (10 rel%) along with the expected isotope patterns, and the base peak of 105 that is typical of aryl ketones, were consistent with the desired product. Tethered ketone **39** was also characterized by ^{1}H-NMR, ^{13}C-NMR, and DEPT spectroscopy. In the ^{1}H-NMR spectrum, the vinylic proton signal was split by two diastereotopic allylic protons (J=7.5 Hz and J=7.0 Hz).



Scheme 2.17 Envisioned Cyclopentadiene Synthesis via Carbonyl Addition.

The catalytic Nozaki-Hiyama-Kishi coupling reaction conditions using 10 mol% of chromium (II) chloride and nickel (II) chloride with 2 equivalents each of manganese (0) metal, chlorotrimethylsilane, and lithium bromide in dimethylformamide at 148 °C resulted in degradation of the tethered ketone starting material **39**. One of the main products of degradation, the alkyne **41** (Figure 2.12), was isolated as a pure pale yellow oil by column chromatography in 28% yield and constituted 53% w/w of the crude mass recovered by standard extraction with petroleum ether. This product of degradation was characterized by ^{1}H-NMR, ^{13}C-NMR, and DEPT spectroscopy. The alkenyl carbon signals at 125.4 ppm and 130.4 ppm, which were present in the ^{13}C-NMR spectrum of the starting material, were absent in this compound and new alkynyl carbon signals at 81.9 ppm and 77.7 ppm were apparent in the ^{13}C-NMR spectrum. In the ^{1}H-NMR spectrum, the diastereotopic protons beta to the ketone shown in Figure 2.12 as H_A and H_B were observed at 3.61 ppm (ddt, J=16.5, 6.5, 2.0, 2.0 Hz) and 2.33 ppm

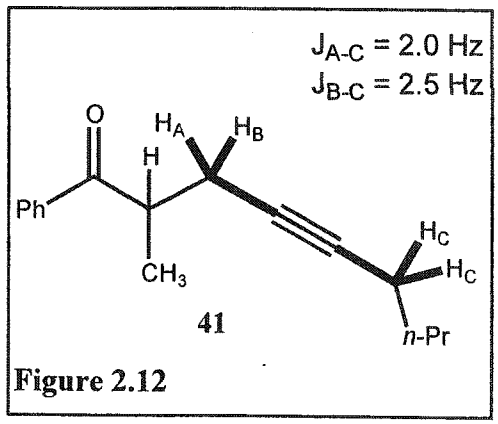


Figure 2.12

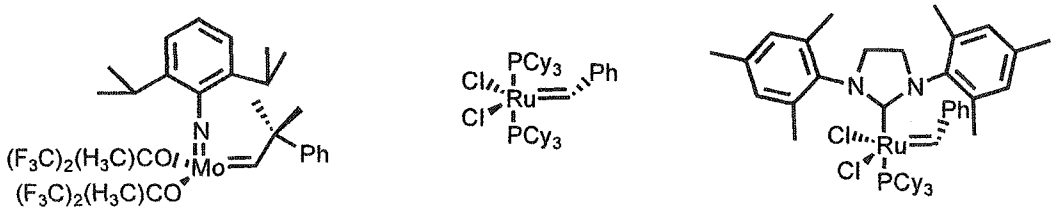
(ddt, J=16.5, 8.1, 2.5, 2.5 Hz) with the typical ^{5}J coupling constants seen in alkyl substituted alkynes of 2.0 Hz and 2.5 Hz.

Therefore, it may be the case that at the higher temperatures necessary for coupling of the vinyl bromide to a ketone, rather than a more reactive aldehyde, loss of the vinyl halide functionality through the formation of an alkyne may be inevitable. Further experiments would be necessary to determine the truth of this conclusion. However, it seems that in practical terms, this carbonyl addition method may be limited to the synthesis of indenes, for which it works well or moderately well even in the case of highly strained and hindered systems.

Chapter 3

Ring-Closing Metathesis Method

3.1 Five-Membered Ring Formation through Ring-Closing Metathesis



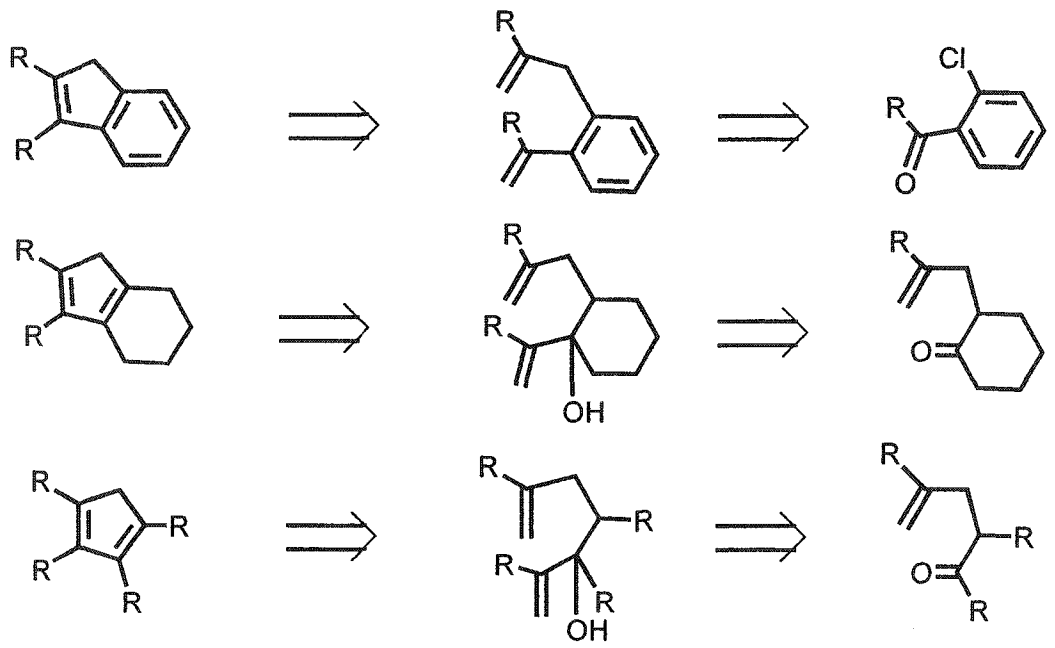
42 Schrock's Catalyst

43 Grubbs' I Catalyst

44 Grubbs' II Catalyst

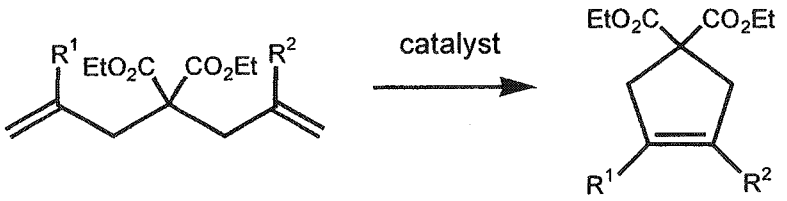
Figure 3.1 Commercially Available Catalysts for Ring-Closing Metathesis

A new and potentially versatile neutral method for forming the double bond of five-membered carbocycle cyclopentadiene derivatives has been introduced with recent advancements in the field of ring-closing metathesis using ruthenium and molybdenum catalysts (Figure 3.1). Although Schrock's catalyst must be stored in a moisture free environment under inert atmosphere, according to a recent report Grubbs' II catalyst may be stored open to the atmosphere without negative impact on the catalyst's activity when it is dispersed in paraffin wax [40]. The ruthenium catalysts show remarkable functional group tolerance and the molybdenum catalyst partial functional group tolerance and both have been applied widely in the synthesis of a variety of natural products. Since the high



Scheme 3.1 Retrosynthetic Approach to Substituted Indenes, Tetrahydroindenes, and Cyclopentadienes from Ketones Through Ring-Closing Metathesis

turnover numbers reported for these catalysts make them a very attractive and increasingly robust synthetic tool [41], as a proof of concept for the use of ring-closing metathesis with Grubbs' and Schrock's type catalysts in the synthesis of metallocene ligands, we have synthesized a substituted indene, tetrahydroindene, and cyclopentadiene using the retrosynthetic strategy shown in Scheme 3.1.

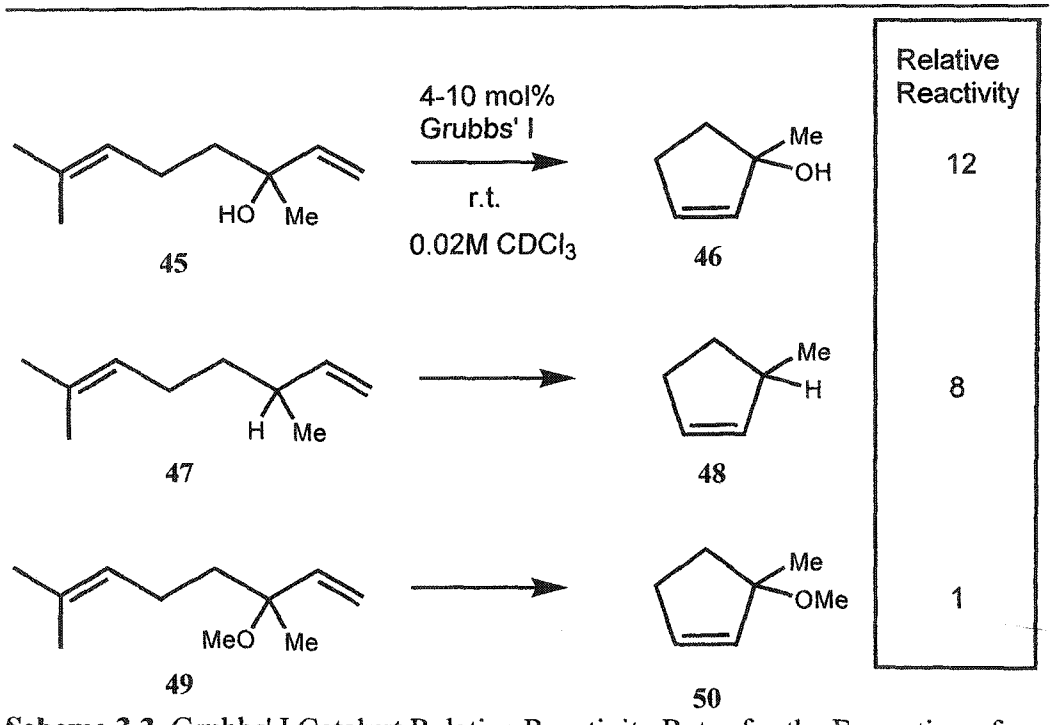


Entry	R^1	R^2	Grubbs' I catalyst	Grubbs' II catalyst	Schrock's catalyst
1	Me	Me	0%	31%	93%
2	*t*-Bu	H	0%	100%	96%
3	Ph	H	25%	---	97%
4	Cl	H	---	96%	---

Scheme 3.2 Five-membered Ring Formation with Grubbs' I , Grubbs' II, and Schrock's Catalysts

Schrock's and Grubbs' II catalysts are known to efficiently form five-membered rings with tetrasubstituted double bonds from the intramolecular metathesis of in less sterically encumbered electron-poor 1,6-diene substrates (Scheme 3.2)[42]. These two catalysts also are known to efficiently form five-membered rings with trisubstituted double bonds from more sterically encumbered or more electron rich 1,6-diene substrates. The Grubbs' I catalyst is generally limited to the formation of five-membered rings with trisubstituted double bonds in less sterically encumbered substrates with electron-poor double bonds.

In the reported literature, Grubbs' I and II catalysts are known for superior performance with substrates containing allylic alcohol groups. In comparing the relative reactivity of Grubbs' I catalyst with substrates containing allylic alcohols and allylic ethers, Hoye found that, while the substrates with



Scheme 3.3 Grubbs' I Catalyst Relative Reactivity Rates for the Formation of a Five-Membered Ring with an Allylic Alcohol or Ether

allylic ethers reacted at a much slower rate than unfunctionalized 1,6-diene, the substrates with allylic alcohol groups actually reacted at a faster rate than the unfunctionalized 1,6-diene (Scheme 3.3)[43]. Hoye conjectured that this effect was caused by the allylic alcohol functionality promoting the "preassociation" of the catalyst with the substrate, either through ligand exchange or hydrogen bonding [43].

While Schrock's catalyst efficiently formed a tetrasubstituted double bond in the presence of a homoallylic alcohol (Figure 3.2), a substrate containing a primary allylic alcohol is reported to have resulted in the catalyst's

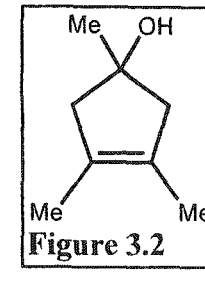
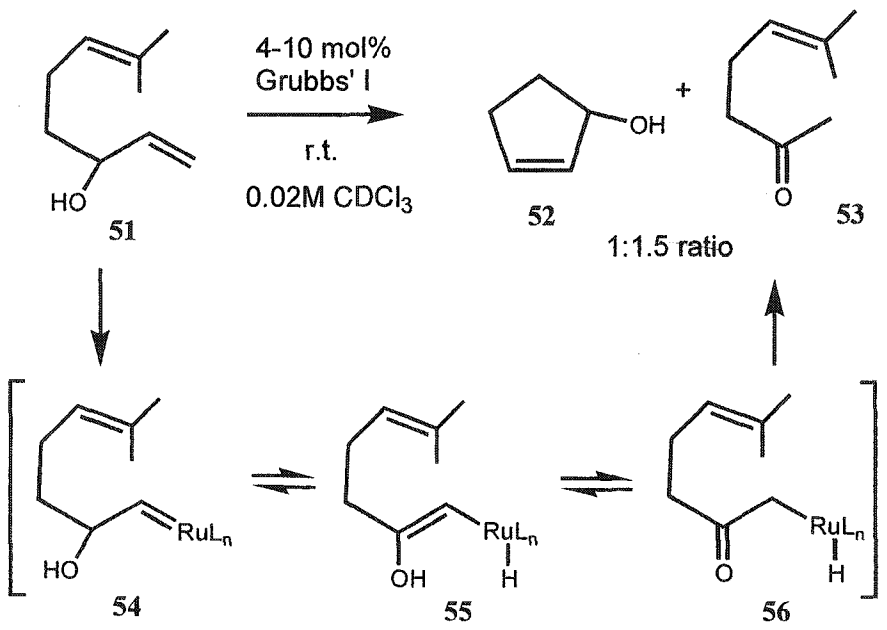
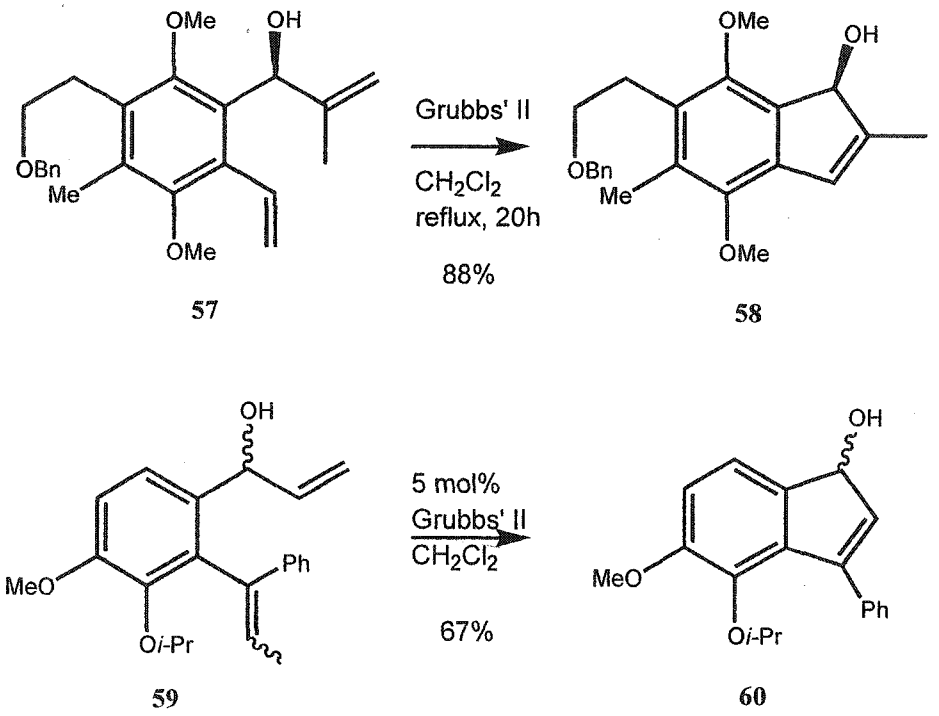


Figure 3.2

decomposition [42d,44]. In addition, a decomposition pathway that leads to a ketone has been reported for Grubbs' I in the presence of a secondary allylic alcohol (Scheme 3.4)[43].

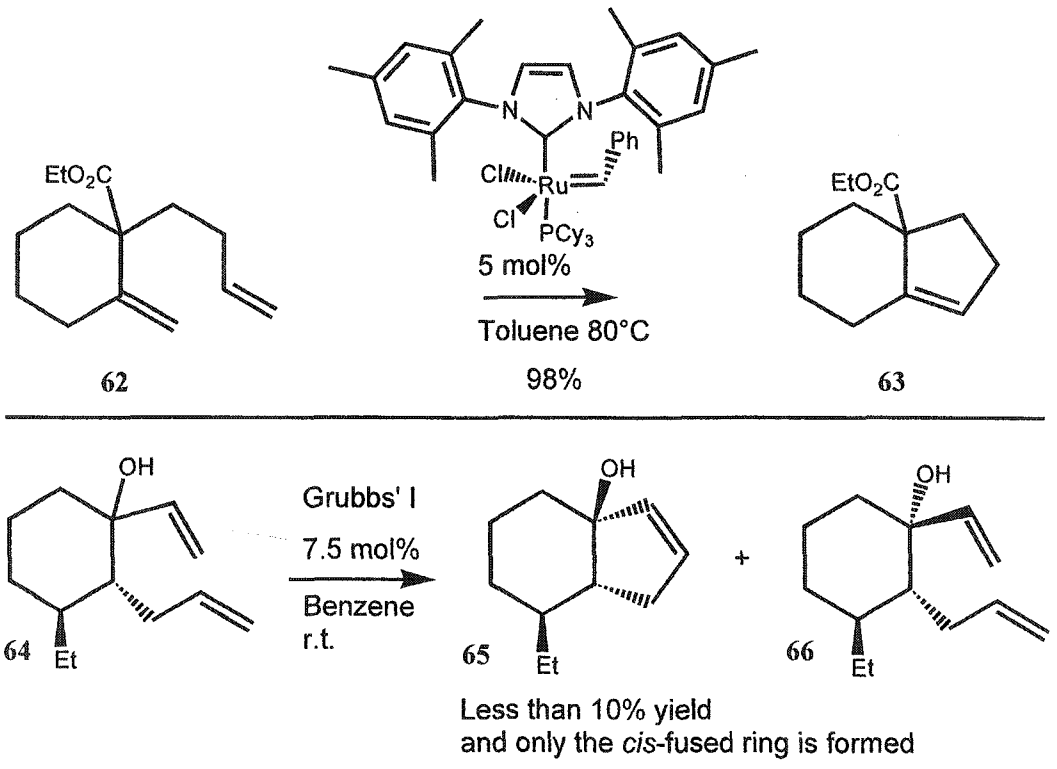


Scheme 3.4 A Secondary Allylic Alcohol Side Reaction with Grubbs' I Catalyst



Scheme 3.5 Syntheses of Indenols with Grubbs' II Catalyst

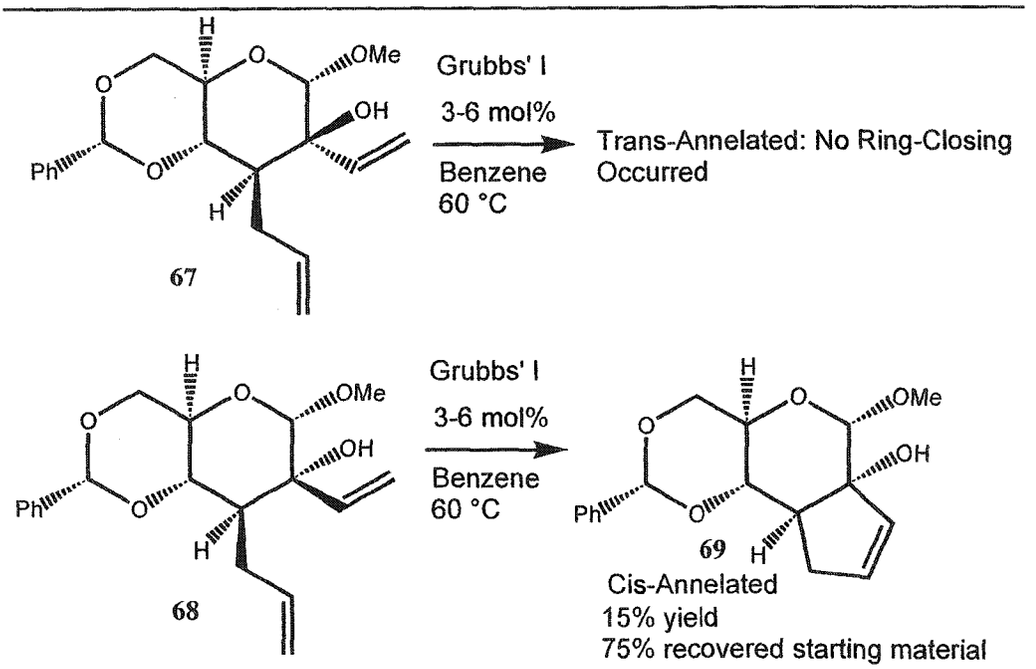
Recently, two natural products with indenol structures have been synthesized through the formation of five-membered rings using Grubbs' II catalyst (Scheme 3.5). Both examples involve the formation of trisubstituted double bonds from substrates with allylic alcohols and proceeded with good yields [45].



Scheme 3.6 Syntheses of Tetrahydroindene Related Compounds via Ring-Closing Metathesis of the 5-Membered Ring

A few compounds related to 4,5,6,7-tetrahydroindene have been synthesized through formation of the five-membered ring with the Grubbs' I and Grubbs' II type catalysts. The ring-closing metathesis forming the [4.0.3] carbocyclic skeletons proceeded only for those substrates that did not have to form a *trans*-fused tetrahydroindene skeleton (Scheme 3.6)[46]. The formation of a similar skeleton with a *trans*-fused ring from compound **67** shown in Scheme 3.7 would not proceed with the Grubbs' I catalyst even with the temperature at 60°C, while the *cis*-fused ring **69** was formed in a low 15% yield with recovery of 75% of the starting material **68** [47]. The *trans*-fused systems are accessible through

ring-closing metathesis with Grubb's I catalyst if the ring being formed is just one carbon larger [47].

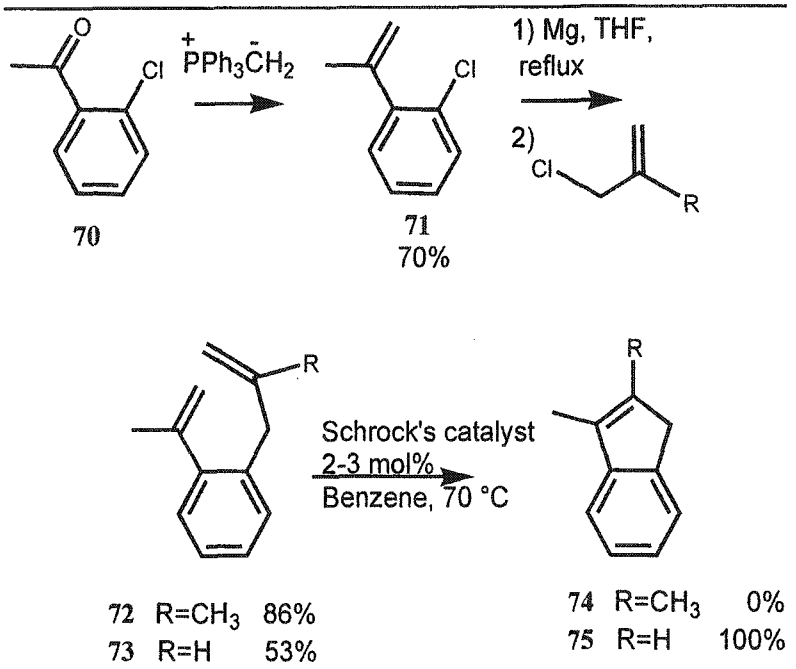


Scheme 3.7 Five-membered Ring Formation in *Cis*- and *Trans*-Fused Systems

3.2 Monosubstituted Indene Synthesis with Schrock's Catalyst

Interest in the applicability of these catalysts to the synthesis of substituted indenes, tetrahydroindenes, and cyclopentadienes led us to conduct a limited but directed screening with several easily accessible substrates derived from readily available ketones. A few examples were known in the literature of Schrock's catalyst successfully forming tetrasubstituted double bonds in five membered rings [42d], so we began with parallel synthetic approaches toward 1H-3-methylindene and 1H-2,3-dimethylindene in which the latter compound required the formation of a tetrasubstituted double bond (Scheme 3.8). The aryl diene starting materials **72** and **73** for the ring-closing metatheses were made in two

steps from 2'-chloroacetophenone. The ketone **70** was readily converted to the 2'-chloro-α-methylstyrene **71** using a standard Wittig olefination. However,



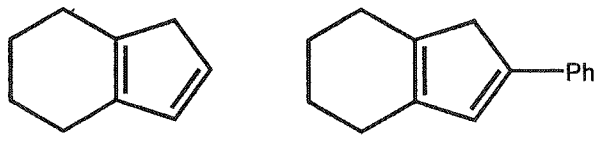
Scheme 3.8 Indene Synthesis via Ring-Closing Metathesis

activation of the aryl chloride **71**, as might be expected, required vigorous reflux with 3.5 equivalents of thoroughly activated magnesium turnings for a period of 24 hours. The cooled Grignard reagent was added to 2.0 equivalents of 3-chloropropene and 3-chloro-2-methylpropene separately. Possibly due to the higher volatility of 3-chloropropene the yield for that reaction was lower (53%) compared to the yield for the 3-chloro-2-methylpropene (86%).

We found that the ring-closing metathesis to form 1H-3-methylindene **75** proceeded quantitatively with the visible evolution of ethene gas through the use of approximately 2.5 mol% of Schrock's catalyst in benzene at 70 °C. The ^{1}H-NMR spectroscopic characterization of the product **75** was identical to the description of 1H-3-methylindene in the literature [48]. In stark contrast, repeated attempts to form 1H-2,3-dimethylindene **74** under the same conditions,

failed entirely resulting with the recovery of unreacted starting material. Thus, we have successfully synthesized a monosubstituted indene in excellent yield through ring-closing metathesis, and while we were unable to synthesize the disubstituted indene, it may be possible that the 1H-2,3-dimethylindene could be formed with a different choice of catalyst, such as one of the Grubbs' second generation catalysts now being reported on widely in the literature [46b].

3.3 Tetrahydroindenes Synthesized with Grubbs' II Catalyst



76 77

Figure 3.3 Tetrahydroindenes via Ring-Closing Metathesis

In a further extension of the proof of concept for this methodology, we were able to synthesize tetrahydroindenes (Figure 3.3) from cyclohexanone in three steps albeit in low yields through the ring-closing metathesis of tethered cyclohexanols such as are shown in Figure 3.4. We chose to use Grubbs' II catalyst in this case, because of literature that suggested that the Grubbs' I catalyst would not be effective in the ring-closure of a *trans*-fused [4.0.3] bicyclic skeleton and because of the relatively robust nature of the Grubbs' II catalyst in the presence of substrates with hydroxyl functionality and the trace amounts of moisture which may accompany them [46,42d]. The fact that the 1,2-diequatorial vinyl and allyl groups were *trans* to

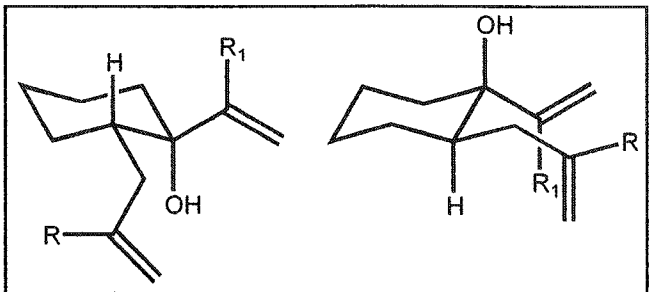
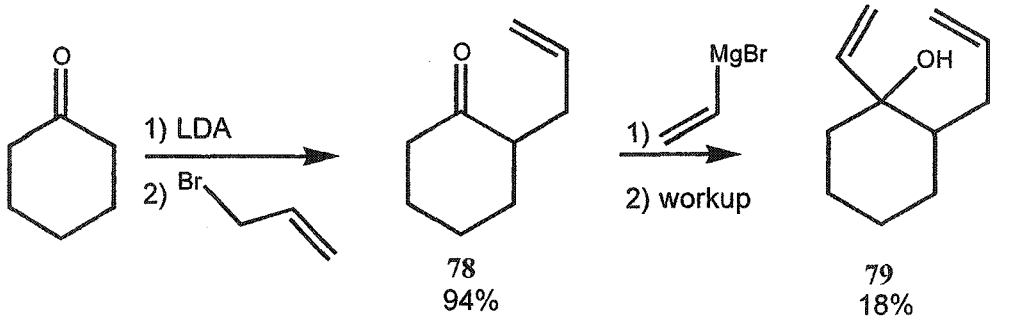


Figure 3.4 Cyclohexanol Substrates.

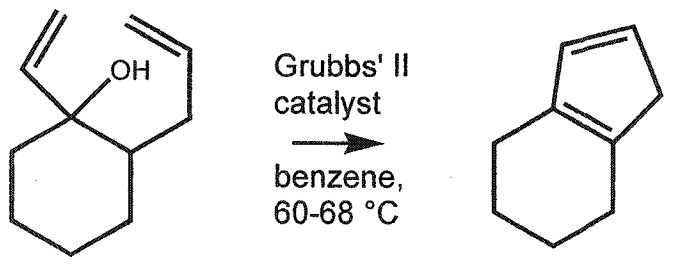
each other on the cyclohexanol ring suggested to us that this ring-closing metathesis, if successful, might be less energetically favorable than one that was not constrained in this manner, so with the intent of not overburdening the system with further substituents on the double bonds, we undertook the synthesis of the often revisited unsubstituted tetrahydroindene [49]. Alkylation of the lithium enolate of cyclohexanone with allyl bromide is well-known in the literature and



Scheme 3.9 Vinyl Grignard Addition to Allylcyclohexanone.

proceeds readily in excellent yield (Scheme 3.9). The 1,2-addition of vinyl Grignard to this ketone resulted in a low unoptimized yield. If 2 equivalents of 1.0 M vinyl magnesium bromide in tetrahydrofuran was added at -78 °C, more starting material was present after workup than when the Grignard reagent was added at higher temperatures, when presumably the yield was low due to the Grignard reagent causing reduction to an alcohol. Since the separation of starting material from the product by column chromatography was more difficult when all the starting material was not destroyed, the higher temperature procedure was preferable. Lower yields for additions to carbonyls are often due to enolization, while these additions could be optimized through the use of cerium trichloride, we had sufficient quantities of the allylic alcohol **79** to execute the metathesis reaction. Usually, 1,2-additions to substituted cyclohexanones such as compound **78** result in mainly *trans*-substituted cyclohexanol [50]. After purification by

column chromatography, there was only one set of signals observed in the ^{13}C-NMR spectrum, this set of signals could correspond to either the *cis*-(*R,S*) and *cis*-(*S,R*) stereoisomers or the *trans*-(*R,R*) and *trans*-(*S, S*) stereoisomers. In all probability, the *trans* stereoisomers of **79** were isolated. The quaternary carbon of the alcohol was observed at 74.7 ppm in the ^{13}C-NMR spectrum. In the ^{1}H-NMR spectrum, the three proton signals from the vinyl group were observed at 5.83 ppm (dd, J=17.0, 10.5 Hz), 5.23 ppm (dd, J=17.0, 1.5 Hz), and 5.07 ppm(dd, J=10.5, 1.5 Hz).



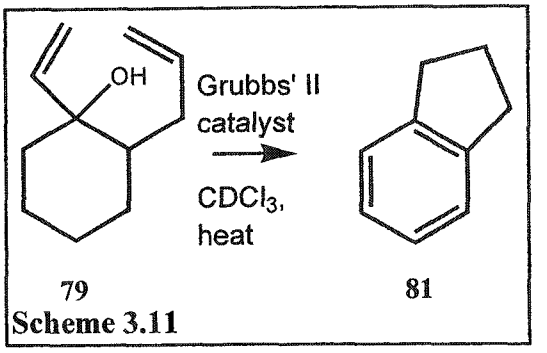
79 **76** 10-19%

Scheme 3.10 Tetrahydroindene Synthesis

For the ring-closing metathesis, 5 mol% of Grubbs' II catalyst was stirred for 18 hours with 100 mg of starting material in benzene-d_6 solvent at 60 °C under argon with a bubbler attached to release any ethene gas. Unlike some other ring-closing metatheses, the release of ethene was not vigorous or even particularly noticeable. After cooling, the mixture was passed through a small amount of silica gel to remove the catalyst and the NMR spectral characterizations were directly obtained in the benzene-d_6 solvent.

A low isolated yield (19%) of the tetrahydroindene which apparently underwent dehydration under these reaction conditions, led us to investigate the possibility of running the reaction in the more volatile chloroform-d_1 solvent

which could be removed under less vacuum. This change to a more acidic solvent, as might have been expected, led to the isolation of indane due to oxidation, instead of tetrahydroindene (Scheme 3.11). To determine whether the yield might be low due to the volatility of tetrahydroindene, we added an equimolar amount of *p*-xylene to the starting material and ran the reaction in benzene-d_6 solvent with 5 mol% Grubbs' II catalyst at 68 °C. After passing the mixture through a small amount of silica gel to remove the catalyst, the ratio of the ^{1}H-NMR spectral signal integrations of the *p*-xylene methyl groups to those of the product signals indicated a mere 10% yield. We concluded, that in the absence of recovered starting material, which we had isolated at times, it seemed probable that the high volatility of the product was causing the apparently low yield. In retrospect, it seems possible that most of the starting material underwent intermolecular metatheses to form oligimers that were removed along with the catalyst, instead of forming the *trans*-fused ring through ring-closing metathesis.

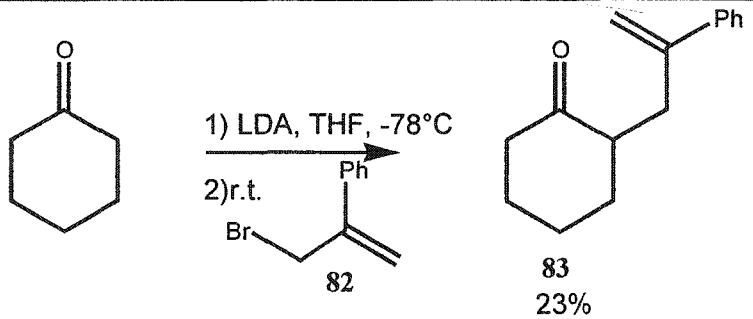


79 81

Scheme 3.11

The isolated tetrahydroindene was characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy. In the ^{1}H-NMR spectrum, bis-allylic geminal proton signal for 1H-4,5,6,7-tetrahydroindene was observed at 2.67 ppm with a slightly more upfield shift in benzene-d_6 than might be seen in chloroform-d_1 solvent. The observation of two inequivalent vinylic protons with signals at 6.36 ppm and 6.20 ppm (J_{cis} = 5.5 Hz) indicated that the less symmetrical tetrahydroindene double bond isomer was the predominant component. The eight protons on the six-

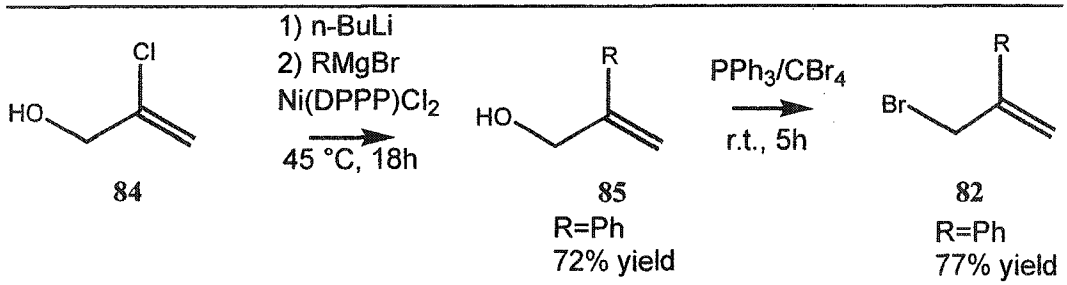
membered ring were observed as two narrow multiplets of 4 protons each at 2.20 ppm and 1.58 ppm. This data is most consistent with ^{1}H-NMR spectral characterization of tetrahydroindene reported by Kloosterziel [49c]. The ^{13}C-NMR spectrum for compound **76** in benzene-d_6 solvent contained signals for four alkenyl carbons at 138.7, 134.8, 129.9, and 128.6 ppm, a bis-allylic carbon at 43.7 ppm, and four alkyl carbons at 25.8, 24.9, 23.9, and 23.7 ppm. Treatment of this compound with *para*-toluenesulfonic acid results in double bond isomerization to the more stable s-*trans* diene.



Scheme 3.12 Alkylation Step in the Synthesis of 2-Phenyltetrahydroindene

Using the same methodology, we were able to synthesize and isolate 1H-2-phenyl-4,5,6,7-tetrahydroindene, a compound also known and characterized in the literature [51]. In this synthesis, we alkylated the lithium enolate of cyclohexanone generated at -78 °C, with 1-bromo-2-phenylprop-2-ene at room temperature (Scheme 3.12). The product of C-alkylation **83** was isolated by column chromatography as a pure yellow oil in an unoptimized 23% yield. The low resolution mass of 214 (15 rel%), the ^{1}H-NMR, ^{13}C-NMR, and DEPT spectral data obtained for this compound were all consistent with this product of monoalkylation. In the ^{13}C-NMR and DEPT spectra, the methine carbon alpha to the ketone was observed at 48.3 ppm and the allylic methylene carbon was

observed at 41.9 ppm. In the ^{1}H-NMR spectrum, the geminal alkene proton signals were observed at 5.35 ppm and 5.10 ppm (J_{gem}= 1.0 Hz).



84

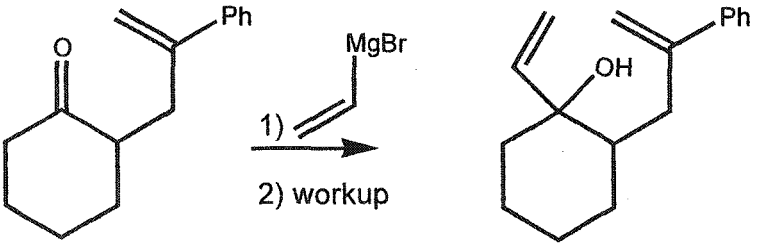
85
R=Ph
72% yield

82
R=Ph
77% yield

Scheme 3.13. Synthesis of the Alkylating Reagent

The alkylating reagent **82** was made in two steps from 2-chloro-2-propen-1-ol **84** using a known Ni-catalyzed cross-coupling reaction followed by bromination (Scheme 3.13)[52]. To achieve a good yield on a larger scale than described in the literature, a larger excess of 2.0 equivalents of phenyl magnesium bromide was added to the lithium alkoxide of **84** with 5 mol% Ni(DPPP)Cl_2, then the mixture was stirred at 45°C overnight. The attraction of this methodology is the potential to modify the substituent by varying the Grignard reagent used in the cross-coupling reaction. Indeed, Organ and Murray have reported coupling procedures for ethyl magnesium bromide and some alkylsilylmethyl magnesium chlorides in addition to their phenyl magnesium bromide procedure. Consequently, the methodology used in our synthesis of 1H-2-phenyl-4,5,6,7-tetrahydroindene could be extended to the synthesis of other 2-substituted tetrahydroindenes of interest. The 2-phenylprop-2-en-1-ol **85** was converted to 1-bromo-2-phenylprop-2-ene **82** by addition to a mixture of triphenylphosphine (2.8 eq.) and carbon tetrabromide (1.4 eq.) in dichloromethane. After stirring for 5 hours at room temperature, removal of the solvent, followed by extraction and

trituration with petroleum ether provided pure 1-bromo-2-phenylprop-2-ene **82** as an orange oil. The ^{1}H-NMR spectral characterization of compound **82** was identical to the literature description [53].



83 **86**

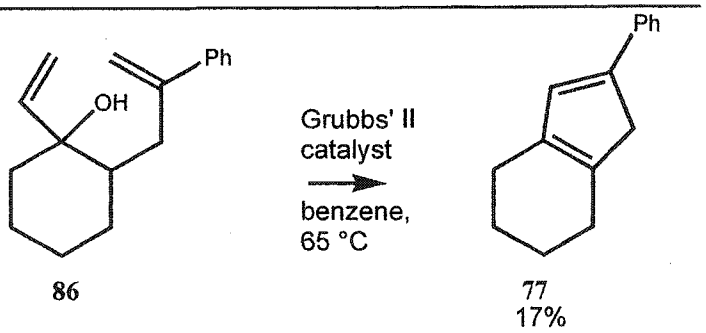
11%

Scheme 3.14 Addition Step in the Synthesis of 2-Phenyltetrahydroindene

As in the previous tetrahydroindene synthesis, the addition of 1.0 M vinyl magnesium bromide in tetrahydrofuran to ketone **83** at room temperature gave a low isolated yield (11%) after column chromatography. A single set of signals was observed in the ^{13}C-NMR spectrum, which would correspond to either the *cis* or the usually more favored *trans* substituted cyclohexanol stereoisomers. The diastereotopic allylic protons were observed in the ^{1}H-NMR spectrum at 2.95 ppm (br d, J_{gem}=14.0 Hz) and 2.14 ppm (dd, J=14.0, 11.0 Hz). The three protons of the vinyl group were observed at 5.89 ppm (J=17.0, 11.0 Hz), 5.37 ppm (J=17.0, 1.5 Hz), and 5.22 ppm (J=11.0, 1.5 Hz). The quaternary carbon bearing the hydroxy group was observed in the ^{13}C-NMR spectrum at 74.6 ppm, the alkyl methine carbon alpha to the alcohol was observed at 41.6 ppm , and the allylic methylene carbon was observed at 39.1 ppm.

The ring-closing metathesis of compound **86**, was performed at 65 °C in a 0.16 M solution of with 5 mol% of Grubbs' II catalyst over 18 hours under argon and resulted in a low unoptimized 17% yield of 1H-2-phenyl-4,5,6,7

tetrahydroindene as colorless crystals (Scheme 3.15). The subtraction of recovered starting material from this yield gave a 26% yield. Presumably the low yield could be due to the reluctance of the trans-fused ring-closing to proceed. This reluctance



86 77 17%

Scheme 3.15 2-Phenyltetrahydroindene Synthesis

presents a problem with this specific synthetic approach and it does not necessarily limit the use of ring-closing metathesis as a tool for the synthesis of tetrahydroindenes, since other approaches that do not require the formation of a five-membered *trans*-fused ring may be envisioned.

The low resolution mass of 196 (100 rel%), ^{1}H-NMR and ^{13}C-NMR spectra of compound 77 corresponded well with the characterization reported by Halterman and Ramsey [51], although the chemical shifts are not directly comparable due to our use of benzene-d_6 rather than chloroform-d_1 solvent. In the ^{1}H-NMR spectrum taken in chloroform-d_1 solvent, the signal for the bis-allylic geminal protons characteristic of these ligands reportedly appears at 3.21 ppm, while we observed them in benzene-d_6 solvent slightly upfield as might be expected at 2.35 ppm. Similarly, we observed the vinylic proton at 6.58 ppm in benzene-d_6 solvent, while the reported value in chloroform-d_1 solvent is 6.65 ppm. The alkyl protons of the six-membered ring were observed as two narrow multiplets at 2.17 ppm and 1.58 ppm with four protons per multiplet. In the ^{13}C-

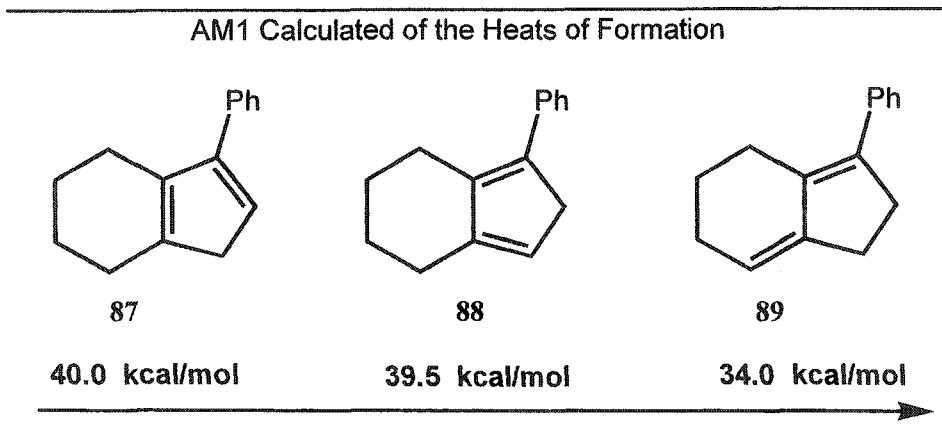
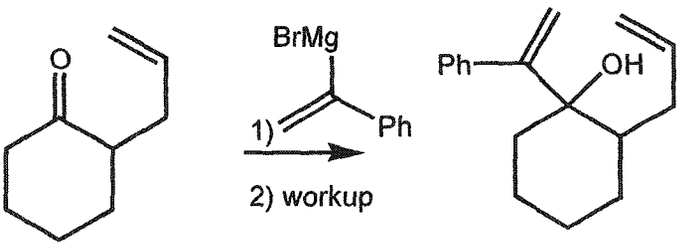


Figure 3.5 AM1 Calculated Tetrahydroindene Heats of Formation

NMR and DEPT spectra, the bis-allylic methylene carbon was observed at 43.6 ppm.

We intended to synthesize 1H-3-phenyl-4,5,6,7-tetrahydroindene to extend the scope of this methodology to 3-substituted tetrahydroindenes (Figure 3.5). However, we encountered a reoccurring difficulty in the syntheses of tetrahydroindenes when the thermodynamically favored rearranged s-*trans* diene **89** was isolated [1, 13]. This problem had been avoided in the synthesis of 1H-2-phenyl-4,5,6,7-tetrahydroindene **77** due to the anchoring effect of the phenyl group in the 2 position. If a group that did not have this conjugation with the double bond were incorporated in the 2 position, then this problem would likely be encountered.

In the preparation of the starting material more the ring-closing metathesis to synthesize 1H-3-phenyl-4,5,6,7-tetrahydroindene, a modest, yet unoptimized improvement over the vinyl Grignard additions in the previous two syntheses was observed, when the addition of an excess of styrenyl Grignard to 2-allylcyclohexanone at room temperature resulted in a 33% isolated yield of

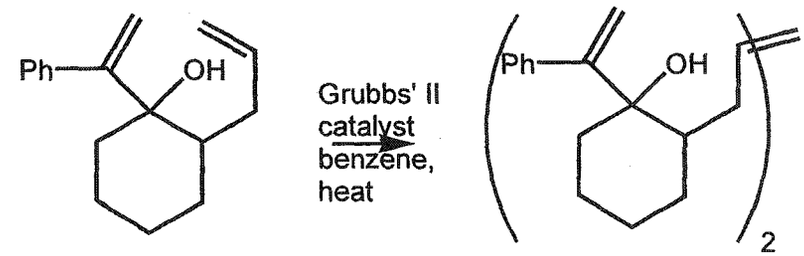


78 **90**
33%

Scheme 3.16 Addition of Styrenyl Grignard Reagent to Allylcyclohexanone

compound **90** after purification by column chromatography and further removal of unreacted starting material by vacuum (Scheme 3.16). The styrenyl Grignard reagent, which has a tendency to homocouple and form 2,3-diphenyl-1,3-butadiene, was prepared in refluxing tetrahydrofuran overnight with equimolar amounts of magnesium turnings and α-bromostyrene. The disubstituted cyclohexanol **90** obtained from this Grignard addition was characterized by electrospray ionization mass spectrometry, ^{1}H-NMR, ^{13}C-NMR, and DEPT spectroscopy. A mass of 265 (89 rel%) consistent with the mass of the $[M+Na]^{+}$ ion was observed. In the ^{1}H-NMR spectrum, the alkenyl protons of the styrenyl group were observed as doublets at 5.56 ppm and 5.12 ppm (J_{gem}=1.5 Hz) and the diastereotopic allylic proton signals appeared at 2.54 ppm and 1.98 ppm (J_{gem}=14.0 Hz). In the ^{13}C-NMR spectrum, the signal for the quaternary carbon bearing the hydroxy group was observed at 77.2 ppm, the alkyl methine carbon alpha to the alcohol was observed at 41.1 ppm, and the allylic methylene carbon was observed at 38.9 ppm.

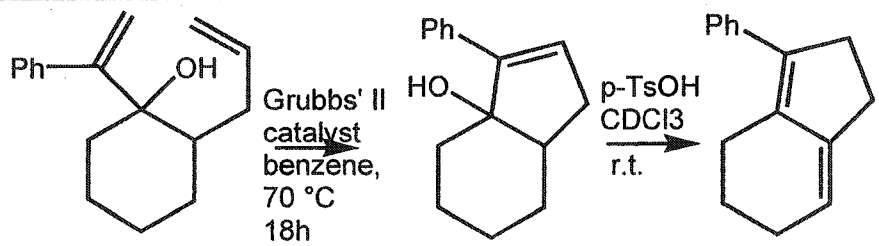
When the ring-closing metathesis was attempted on compound **90** at approximately the same dilution as the previous two syntheses, 0.15-0.3M in



90 **91**

Scheme 3.17 Dimer Formed from Olefin Metathesis

benzene-d_6 solvent with 5 mol% of Grubbs' II catalyst, the only isolable product was the intermolecular metathesis dimer **91** shown in Scheme 3.17. This dimer was characterized by electrospray ionization mass spectrometry, ^{1}H-NMR, ^{13}C-NMR, and DEPT spectroscopy. A mass of 479 (100 rel%) consistent with the mass of the $[M+Na]^+$ ion was observed. The ^{1}H-NMR spectral signals had a broadened appearance due to an apparent mixture of (*E*)- and (*Z*)-stereoisomers. The geminal alkenyl protons from the styrenyl groups were observed at 5.46 ppm and 5.02 ppm (J_{gem} = 2.0 Hz), while the other vinylic protons were observed at 5.35 ppm. In the ^{13}C-NMR spectrum, evidence for an approximately 1:1 ratio of (*E*)- and (*Z*)-stereoisomers was apparent, as two distinct peaks of approximately equal intensity were seen for the quaternary carbons bearing the hydroxy group (77.34, 77.31 ppm), for the alkyl methine carbons alpha to the alcohol (41.58, 41.55 ppm), and the allylic methylene carbons (38.92, 38.87 ppm), while other signals were overlapped, such as the single signal at 114.1 ppm for all the styrenyl methylene carbons, which are symmetry equivalent in both isomers.

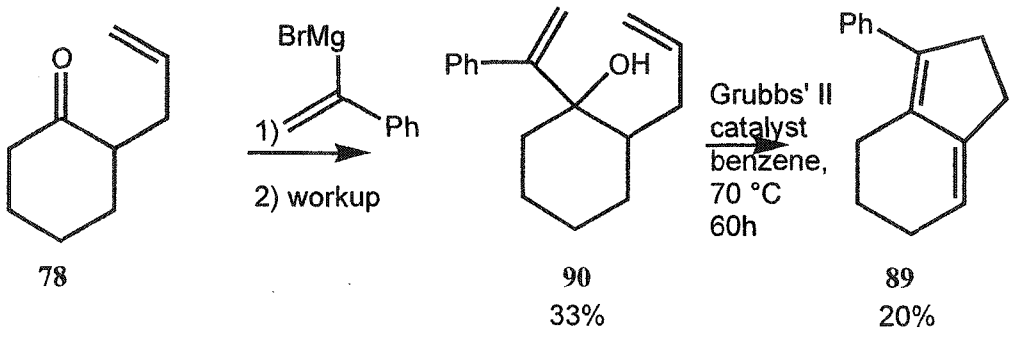


90 **92** **89**

Scheme 3.18 Isolation of Ring-Closed Alcohol and Dehydration.

The ring-closing metathesis of compound **90** was conducted with more dilute conditions, 0.01 M in distilled benzene, over 18 hours at 70 °C with 8 mol% of Grubbs' II catalyst under argon, and this resulted in the isolation of the ring-closed alcohol **92**, shown in Scheme 3.18, which was subsequently converted to the thermodynamically stable s-*trans* diene **89** by treatment with *para*-toluenesulfonic acid. In the ^{1}H-NMR spectrum of alcohol **92**, the vinylic proton was observed at 6.06 ppm (dd, J=2.0, 2.5 Hz) and the two allylic protons appeared as a multiplet at 2.25 ppm. In the ^{13}C-NMR spectrum, the signal for the quaternary carbon bearing the hydroxy group was observed at 81.9 ppm, the signal for the methine alpha to the alcohol was observed at 50.2 ppm. More evidence would be needed to stipulate whether this ring-closing metathesis with Grubbs' II catalyst had led to the *trans*-fused or *cis*-fused compound.

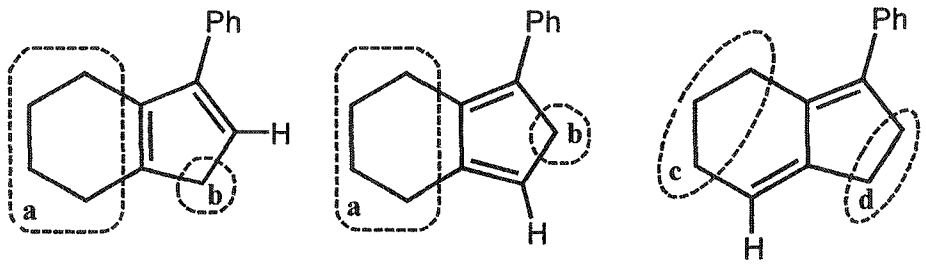
Some ^{1}H-NMR spectroscopic evidence of the desired 1H-3-phenyl-4,5,6,7-tetrahydroindene **87** was observed for a reaction that was run on a scale too small for gathering ^{13}C-NMR spectral data, so we again ran the reaction under the dilute conditions, this time for 60 hours in an effort to ensure elimination would occur (Scheme 3.19). These conditions resulted in a 20% isolated yield of the more stable rearranged s-*trans* diene **89**.



78 **90** 33% **89** 20%

Scheme 3.19 Synthesis of 3-Phenyltetrahydroindene Rearranged Isomer

The low resolution mass of 196 (100 rel%), ^{1}H-NMR, COSY, and ^{13}C-NMR spectroscopic characterization for this compound were all consistent with the structure of s-*trans* diene **89**. The vinylic proton was observed at 5.56 ppm in the ^{1}H-NMR spectrum as a finely split multiplet. In the ^{13}C-NMR spectrum, the alkenyl methine carbon was observed at 116.6 ppm, and the four allylic methylene carbons were observed at 33.2, 27.2, 25.6, and 25.1 ppm.



87 **88** **89**

a) Isolated spin system with 8 protons
b) 2 proton spin system coupled to a vinylic proton signal

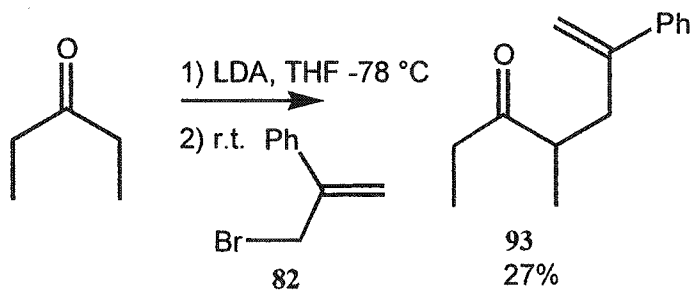
Versus

c) 6 proton spin system coupled to the vinylic proton signal
d) Isolated spin system with 4 protons

Scheme 3.20 Diagnostic COSY Coupling Patterns

In the COSY spectrum, two separate spin systems (**c** and **d** in Scheme 3.20) were evident for the alkyl protons. One of these spin systems consisted of four protons while the other consisted of six protons. The six proton spin system was coupled to the vinylic proton signal, while the four proton spin system was isolated. This coupling data is consistent with the structure of the s-*trans* diene **89**, and is not consistent with either of the desired tetrahydroindenes **87** or **88**, because for these compounds an isolated spin system of eight protons and a two proton spin system coupled to a vinylic proton would be expected (**a** and **b** in Scheme 3.20).

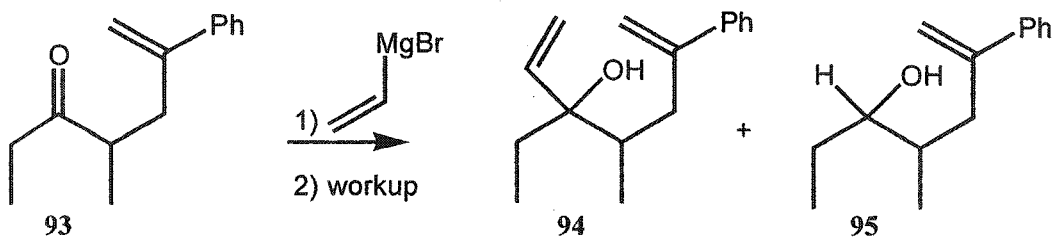
3.4 Trisubstituted Cyclopentadiene Synthesized with Grubbs' II Catalyst



Scheme 3.21 Alkylation of 3-Pentanone

In a further extension of the scope, we have as a proof of concept used this methodology to synthesize a 1,2,4-trisubstituted cyclopentadiene. Alkylation of the lithium enolate of 3-pentanone generated at -78 °C with 1-bromo-2-phenylprop-2-ene **82** at room temperature resulted in 27% isolated yield of the C-alkylation product **93** after column chromatography. The low resolution mass of 203 (100 rel%), which corresponds to the $[M+H]^+$ ion, along with the ^{1}H-NMR, ^{13}C-NMR, and DEPT spectral data confirmed that this compound was the product of monoalkylation. In the ^{1}H-NMR spectrum, the two diastereotopic allylic protons had signals at 2.86 ppm and 2.34 ppm (J_{gem} = 14.0 Hz) and were coupled to the proton alpha to the ketone, which was observed at 2.54 ppm (ddq, J=6.5, 6.5, 7.0 Hz). In the ^{13}C-NMR and DEPT spectra, the methine carbon alpha to the ketone was observed at 44.0 ppm.

The addition of 1.5 equivalents of 1.0 M vinyl magnesium bromide in tetrahydrofuran to the tethered ketone **93** at 25 °C gave 30% isolated yield of



93 94 95

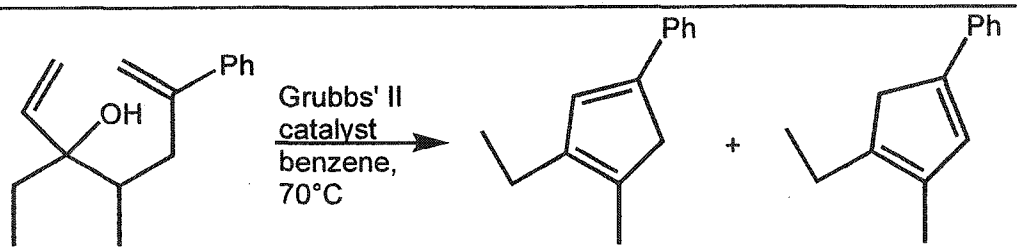
30% yield of desired product

31% reduced starting material

Scheme 3.22 Addition of Vinyl Grignard Reagent

the desired addition product **94** and 31% isolated yield of side product **95**, due to the reduction of the ketone to an alcohol, after column chromatography (Scheme 3.22). The ^{1}H-NMR, ^{13}C-NMR and DEPT spectral characterization of compound **94**, showed a 1:1.3 ratio of diastereomers had been isolated. The characteristic geminal coupling constants (J=14.5 Hz, and J=14.0 Hz) for the allylic protons of these two diastereomers were distinguishable as observed in the signals at 3.11 and 2.99 ppm respectively. In the ^{13}C-NMR and DEPT spectra, all the signals for the two diastereomers appeared separately except for the quaternary carbon bearing the hydroxy group (77.9 ppm) and the carbons of the phenyl group. The carbons of the vinyl groups in these diastereomers were observed as methine signals at 142.4 and 141.3 ppm and methylene signals at 113.51 and 113.48 ppm.

In marked contrast to the tetrahydroindene ring-closing metatheses, when the acyclic starting material **94**, 0.2 M in benzene, was added to the 5 mol% of Grubbs' II catalyst, ethene was evolved in the first 15 minutes in such volume as to cause vigorous foaming of the solvent. After stirring for 48 hours at 70 °C, the two desired cyclopentadiene isomers **96a** and **96b** were isolated by column chromatography as a 1:1.7 ratio of double bond isomers in 35% yield. The low



94 96a 1.7:1.0 ratio 96b

35%

Scheme 3.23 Synthesis of a Substituted Cyclopentadiene via Ring-Closing Metathesis

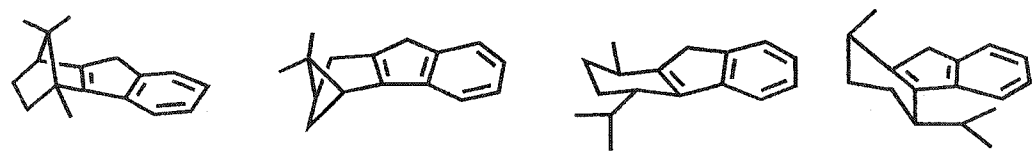
resolution mass of 184 (100 rel%), the ^{1}H-NMR, ^{13}C-NMR, and DEPT spectral data were all consistent with the formation these cyclopentadiene isomers. The characteristic bisallylic geminal protons were observed in the ^{1}H-NMR spectrum at 3.37 and 3.35 ppm for the major and minor isomers respectively. A single vinylic signal was observed for the major isomer at 6.74 ppm and for the minor isomer at 6.83 ppm. In the ^{13}C-NMR and DEPT spectra, the bisallylic methylene carbons were observed at 45.3 and 42.5 ppm and the alkenyl methine carbons were observed at 131.7 and 130.0 ppm. None of the steps in the synthesis of this cyclopentadiene were optimized, but the synthesis represents a proof of concept for a method that seems promising for the synthesis of a variety of substituted cyclopentadienes.

Through the use of ring-closing metathesis to form trisubstituted double bonds in five-membered rings, we have been able to synthesize monosubstituted indene, monosubstituted tetrahydroindene, and 1,2,4-trisubstituted cyclopentadiene from readily available ketones. Difficulties in the synthesis of the substituted tetrahydroindenes were encountered that are instructive for the design of future approaches to these ligands through ring-

closing metathesis. Since this methodology is relatively new and currently under wide research, it seems likely that the low yields we have reported here for the ring-closing reactions could see some improvements in the future, making this a very promising tool for regioselective syntheses of these desirable ligands.

Conclusion

During the course of our research, we applied the Cr(II)-mediated, Ni(II)-catalyzed carbonyl addition method for the synthesis of indenes, which was developed by Halterman and Zhu in a new application of the Nozaki-Hiyama-Kishi coupling reaction, to the synthesis of chiral annelated indenes in three steps from readily available chiral ketones: (1*R*)-(+)-camphor, (1*R*,5*S*)-(+)-nopinone, and (-)-menthone. The synthesis of the camphor annelated indene **4** was the most

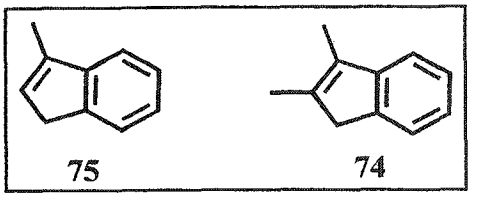


4 **5** **6a** **6b**

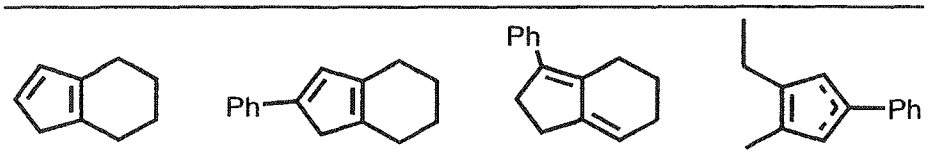
successful. This camphor annelated indene was reliably synthesized as pure oil with an overall yield of 42%. The synthesis of the pinanyl indene **5** was less reliable with a lower overall yield of 26% due to a tendency for the Cr(II)-mediated, Ni(II)-catalyzed coupling to proceed intermolecularly rather than intramolecularly. When we undertook the synthesis of menthone annelated indene, we found that the coupling conditions caused epimerization of the chiral center bearing an enolizable proton. Consequently, a 2:1 mixture of the *trans*- and *cis*-menthyl annelated indenes **6a** and **6b**, which were not separable by column chromatography, was obtained in 38% overall yield. We attempted the extension of this method to the synthesis of substituted cyclopentadienes, but were unsuccessful due to several difficulties.

We also executed a proof of concept for the use of ring-closing metathesis with Grubbs' II and Schrock's catalysts as a new method for forming

the five-membered rings of substituted indenes, cyclopentadienes, and tetrahydroindenes. We found that Schrock's catalyst quantitatively formed the trisubstituted olefin in the five-membered ring of 1H-3-methylindene **75**, but did not form the tetrasubstituted olefin of the five-membered ring of 1H-2,3-dimethylindene **74**. We also synthesized known ligands, 1H-4,5,6,7-tetrahydroindene **76** and 1H-2-phenyl-4,5,6,7-tetrahydroindene **77**, through ring-closing metathesis with Grubbs' II catalyst. However, we found that the yields were very low due to the reluctance of the ring-closure to form a *trans*-fused [4.0.3] ring system. In addition, the formation of thermodynamically favored s-*trans* diene double bond isomers was problematic and resulted in the isolation of compound **89**, instead of the desired 1H-3-phenyl-4,5,6,7-tetrahydroindene, a ligand that has not been reported in the literature. We also successfully synthesized a trisubstituted cyclopentadiene, 1-ethyl-2-methyl-4-phenylcyclopenta-1,3-diene **96**, with unoptimized yields and found that the ring-closure of this unannelated compound was very facile. We conclude that this new ring-closing metathesis methodology is a promising method for the synthesis of a variety of highly-substituted metallocene ligands.



75 **74**



76 **77** **89** **96**

Experimental

General:

The molarity of the *n*-butyllithium in hexanes was determined by titration of diphenylacetic acid in dry tetrahydrofuran. Diisopropylamine was distilled under nitrogen from sodium hydroxide pellets and stored under nitrogen. When tetrahydrofuran, benzene, diethyl ether, and hexanes were used as dry solvents, they were distilled from sodium metal in the presence of benzophenone under nitrogen. Dichloromethane was distilled from calcium hydride under nitrogen. N-Bromosuccinimide was recrystallized (1 g/10 mL) in water and dried under vacuum in the presence of calcium chloride or phosphorous pentoxide. The dry benzene-d_6 solvent used in the ring-closing metathesis reactions was distilled from sodium metal in the presence of benzophenone under argon and stored in a nitrogen glovebox. The Nozaki-Hiyama-Kishi coupling reactions were performed with dimethyl formamide solvent that had been freshly distilled under house vacuum from 4 Å molecular sieves and stored under nitrogen on 4 Å molecular sieves for no longer than one month.

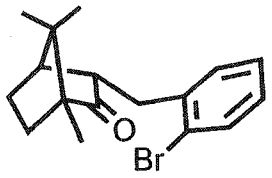
Chromium (II) chloride, Schrock's and Grubb's II catalysts were used as received from Strem Chemicals and stored in a nitrogen glovebox. Grubb's II catalyst was also used as received from Sigma-Aldrich. (+)-Nopinone was synthesized using a literature method [54]. α-Bromostyrene was synthesized using a literature method [55].

AM1 calculations were run with MacSpartan Plus (1996) software (Wavefunction Inc., Irvine, CA.).

Compound **4**: Listed following compound **8**.

Compound **5**: Listed following compound **11**.

Compounds **6a/6b**: Listed following compound **12**.



References: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448.

Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

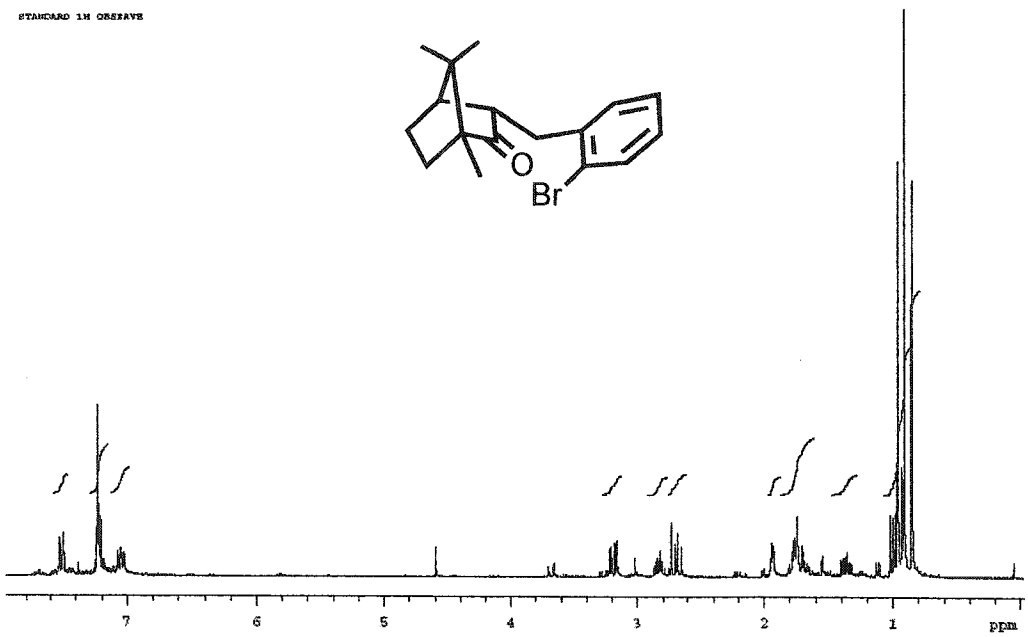
2-(2-Bromobenzyl)-camphor (7): Distilled tetrahydrofuran (47 mL) was added to a dry 250 mL flask under nitrogen containing distilled diisopropylamine (0.020 mol, 2.8 mL). The solution was cooled to -78 °C with a dry ice/acetone bath, then *n*-butyllithium (0.019 mol, 7.6 mL, 2.5 M in hexane) was added dropwise via syringe. The mixture was allowed to warm to 0 °C over 30 min, then was returned to -78 °C while a solution of (R)-(+)-camphor (0.016 mol, 2.4 g) in tetrahydrofuran (4 mL) was added dropwise by syringe. The pale yellow solution was warmed to room temperature while stirring for 2 h, then a solution of 2-bromobenzylbromide (0.026 mol, 6.4 g) in distilled tetrahydrofuran (20 mL) was rapidly added via syringe to the enolate solution. After stirring under nitrogen overnight, the mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with sodium sulfate and concentrated under vacuum. To purify, solid camphor was removed by filtration, then a shortpath distillation was used to remove remaining

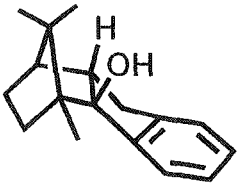
excess 2-bromobenzylbromide leaving the product as a yellowed oil (0.0123 mol, 3.94 g, 77%). Inspection of the ^{1}H-NMR spectrum indicated compound 7 was about 80% pure.

HRMS (TOF ES+, rel.%): 345.0792 (44.3%, $[(M+2)+Na]^+$), 343.0764 (49.2%, $[M+Na]^+$), 323.0944 (26.0%, $[(M+2)+H]^+$), 321.0934 (25.0%, $[M+H]^+$). $[M+Na]^+$ calcd for $C_{17}H_{21}BrO$, 343.0673.

MS (EI, 70 eV, rel.%): 321(4, M^+), 241(100, loss of Br$^\cdot$), 95(13).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.53(d, J=7.5 Hz, 1H), 7.24(m, 2H), 7.06 (ddd, J=3.0, 6.0, 7.5 Hz, 1H), 3.20(dd, J=14.0 , 4.5 Hz, 1H), 2.84 (ddd, J=10.0, 4.5, 4.0 Hz, 1H), 2.71 (dd, J=14.0, 10.0 Hz, 1H), 1.95 (br dd, J=4.0, 3.5 Hz, 1H), 1.80-1.66 (m, 3H), 1.40 (m, 1H), 0.98(s, 3H), 0.93(s, 3H), 0.87(s, 3H).





References: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448.

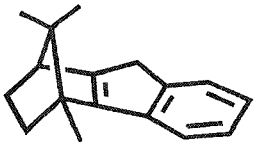
Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

Camphor Annelated Indanol (8): A dry 100 mL roundbottomed Schlenk flask was charged with chromium (II) chloride (0.0406 mol, 5.00 g) and nickel (II) chloride (0.00059 mol, 0.076 g) under inert atmosphere. Dimethylformamide (30 mL), recently distilled from molecular sieves, was added to the flask under argon and the dark green solution was vigorously stirred. In a dry 25 mL flask, 2-(2-bromobenzyl)-camphor 7 (0.014 mol, 4.5 g) was placed under argon, then diluted in distilled dimethylformamide (12 mL) and transferred via syringe to the metal salt solution. The solution was left stirring in 125 °C oil bath for 16 h under argon, then cooled and quenched with water and extracted with copious amounts of dichloromethane, which were combined and washed with water and brine, dried with magnesium sulfate, and concentrated under vacuum to a crude brown oil (2.2 g). Column chromatography (silica gel, CH_2Cl_2) was used to isolate the camphor annelated indene **4** (0.00065 mol, 0.145 g) and camphor annelated indanol **8** (0.0069 mol,1.68 g) for a 54% yield.

HRMS (TOF ES+) $[M+Na]^+$ calcd for $C_{17}H_{22}O$, 265.1568; found 265.1742.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.16-7.35 (m, 4H), 3.10 (dd, J=9.5, 17.0 Hz, 1H), 3.00 (dddd, J=1.5, 2.0, 5.0, 9.5 Hz, 1H), 2.71 (dd, J=2.0, 17.0 Hz, 1H), 1.82 (s, 1H), 1.80 (t, J=5.0, 5.0 Hz, 1H), 1.36 (dddt, J=2.0, 3.0, 4.5, 12.0, 12.0 Hz, 1H),

1.25 (s, 3H), 1.23 (dt, J=4.5, 12.0, 12.0 Hz, 1H), 1.14 (s, 3H), 0.94 (m, 1H), 0.91 (s, 3H), 0.62 (ddd, J=3.0, 9.5, 12.0 Hz, 1H).



References: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448.

Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

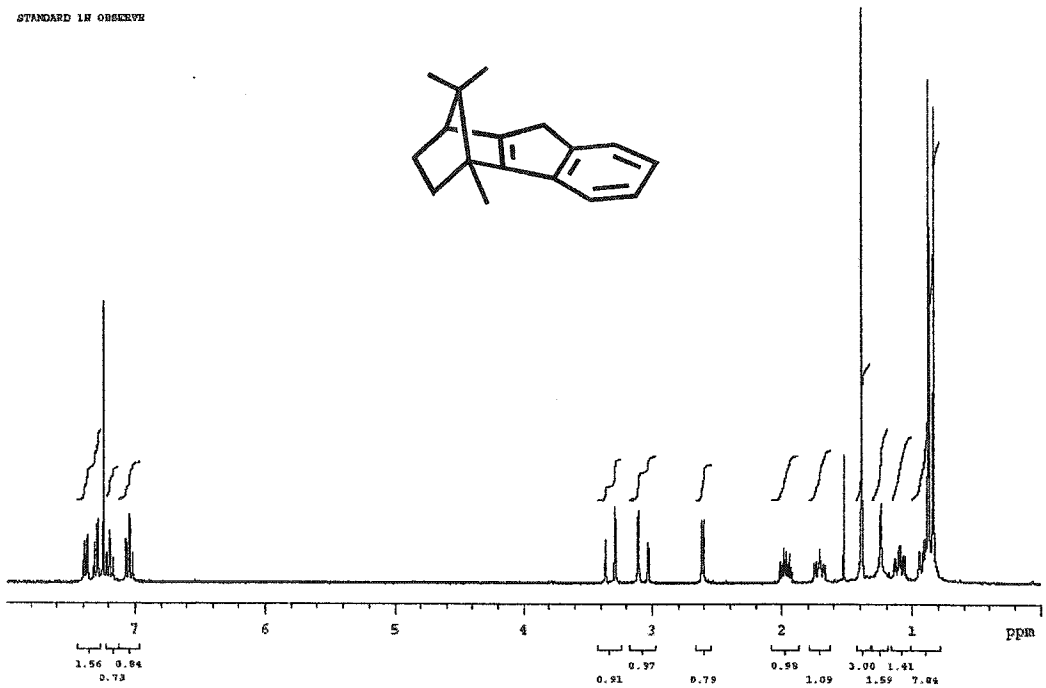
Camphor Annelated Indene (4): Benzene (30 mL), triethylamine (0.081 mol, 8.2 g), and the camphor annelated indanol **8** (0.016 mol, 3.9 g) were placed in a 100 mL flask with a reflux condenser attached. The mixture was flushed with nitrogen and cooled to 0 °C in a wet ice bath, then methanesulfonyl chloride (0.025 mol, 1.9 mL) was added dropwise via syringe. The solution was allowed to stir for 1.5 h, then was brought to a reflux for 16 h. Since TLC analysis revealed some starting material remained, the solution was again cooled to 0 °C and another portion of methanesulfonyl chloride (1.0 mL) was added dropwise via syringe. After stirring for 1.5 h, the solution was left at reflux over the weekend. The mixture was quenched with water and extracted with three portions of diethyl ether. The combined organic phase was washed repeatedly with water, dried with magnesium sulfate, and concentrated under vacuum to a brown oil (3.7 g, 100% yield). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **4** was greater than 95% pure.

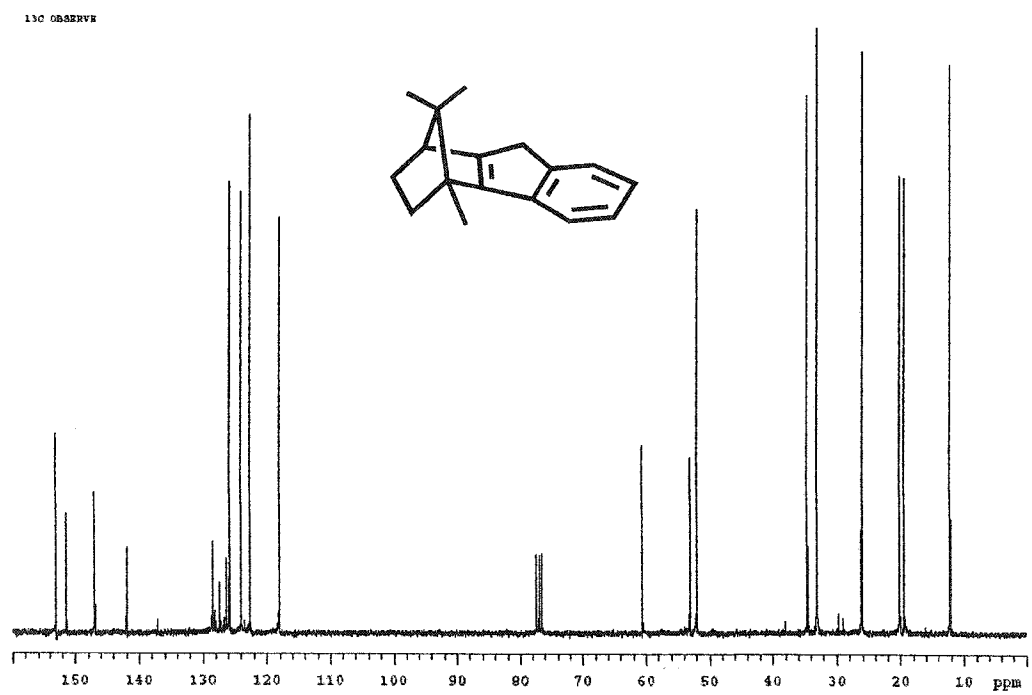
MS (EI, 70 eV, rel %): 224 (90, M^{+}), 181 (100), 179 (76), 165 (69), 91 (16).

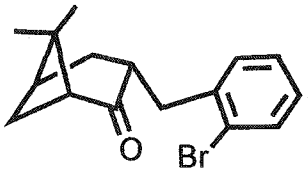
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37 (d, J=7.5 Hz, 1H), 7.30 (d, J=7.5 Hz, 1H), 7.19 (dd, J=7.5, 7.5 Hz, 1H), 7.04 (dd, J=7.5, 7.5 Hz, 1H), 3.31 (d, J=23 Hz, 1H), 3.07 (d, J=23 Hz, 1H), 2.60 (d, J=3.5 Hz, 1H), 1.97 (dddd, J=12.0, 8.5, 3.5,3.5 Hz, 1H), 1.71 (br ddd, J=12.0, 8.5, 3.5 Hz, 1H), 1.39 (s, 3H), 1.09 (ddd, J=12.0, 9.0,

3.5 Hz, 1H), 0.91 (ddd, J= 12.0, 9.0, 3.5 Hz, 1H), 0.87 (s, 3H), 0.83 (s, 3H).

(300 MHz, $CDCl_3$, DEPT) δ: 153.3(C), 151.7(C), 147.3(C), 142.3(C), 126.2(CH), 124.4(CH), 123.0(CH), 118.4(CH), 61.0(C), 53.4(C), 52.4(CH), 34.9(CH_2), 33.5(CH_2), 26.4(CH_2), 20.5(CH_3), 19.8(CH_3), 12.5(CH_3).







Reference: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448.

Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

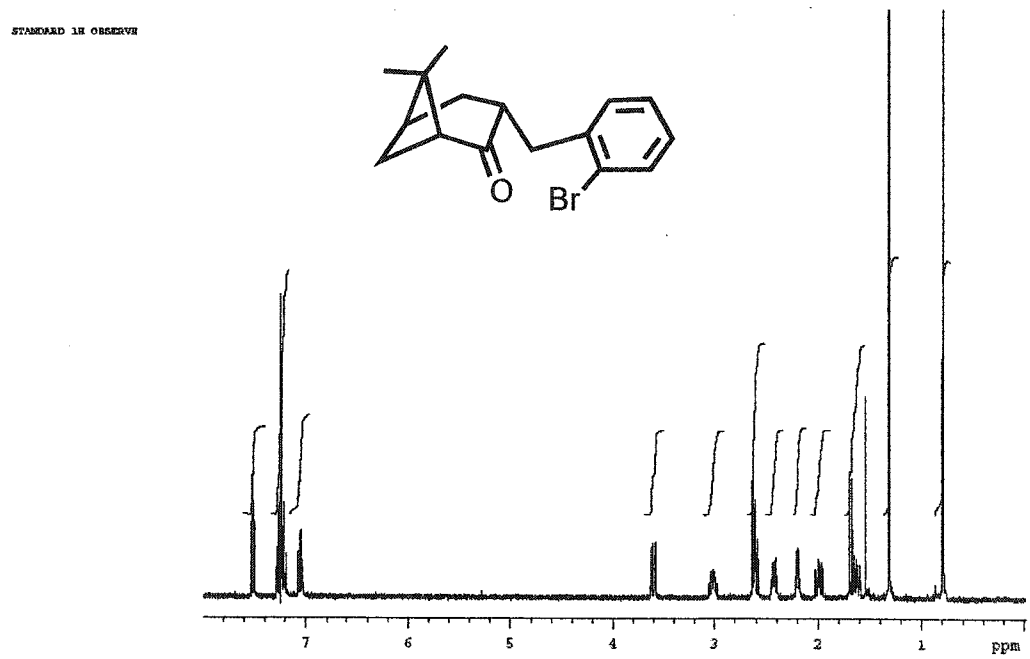
2-(2-Bromobenzyl)-nopinone (11): Distilled tetrahydrofuran (45 mL) was added to a dry 250 mL flask under nitrogen containing distilled diisopropylamine (0.020 mol, 2.8 mL). The solution was cooled to -78 °C with a dry ice/acetone bath, then *n*-butyllithium (0.018 mol, 9.2 mL, 2.00 M in hexane) was added dropwise via syringe. The mixture was allowed to warm to 0 °C over 30 min, then was returned to -78 °C while (+)-nopinone (0.016 mol, 2.2 g) was added dropwise by syringe. The orange solution was warmed to room temperature while stirring for 2 h, then a solution of 2-bromobenzylbromide (0.0257 mol, 6.42 g) in distilled tetrahydrofuran (18 mL) was rapidly added via syringe to the enolate solution. After stirring under nitrogen overnight, the mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with sodium sulfate and concentrated under vacuum. The product is a white solid, that may be purified by recrystallization or column chromatography (SiO_2, 3:1 petroleum ether/diethyl ether) (0.010 mol, 3.2 g, 65% yield). Mp 117-120°C. Inspection of the ^{1}H-NMR spectrum indicated compound **11** was greater than 95% pure.

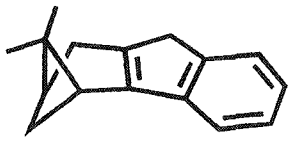
HRMS (TOF ES+, rel.%) 331.0537 (8.2%, $[(M+2)+Na]^+$), 329.0495 (7.6%, $[M+Na]^+$), 309.0737 (13.2%, $[(M+2)+H]^+$) 307.0756 (11.9%, $[M+H]^+$). $[M+Na]^+$

calcd for $C_{16}H_{19}BrO$, 329.0517.

MS(EI, 70 eV, rel %) 307(12, M^+), 227(100, loss of $Br^·$), 171(26), 157(21), 95 (20).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, J=8.0 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.21 (dd, J=8.0, 8.0 Hz, 1H), 7.05 (dd, J=8.0, 8.0 Hz, 1H), 3.60 (dd, J=13.5, 4.5 Hz, 1H), 3.01 (ddd, J=10.0, 8.5, 4.5 Hz, 1H), 2.62 (dd, J=5.0, 5.0 Hz 1H) 2.60 (dd, J=13.5, 10.0 Hz 1H), 2.42 (ddd, J=10.0, 5.0, 5.0 Hz, 1H), 2.19 (ddd, J=4.5, 5.0, 5.0 Hz, 1H), 1.99 (ddd, J=13.5, 10.0, 4.5 Hz, 1H), 1.68 (d, J=10.0 Hz, 1H),1.62 (dd, J=13.5, 8.5 Hz, 1H) 1.31 (s, 3H), 0.79 (s, 3H).





References: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448.

Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

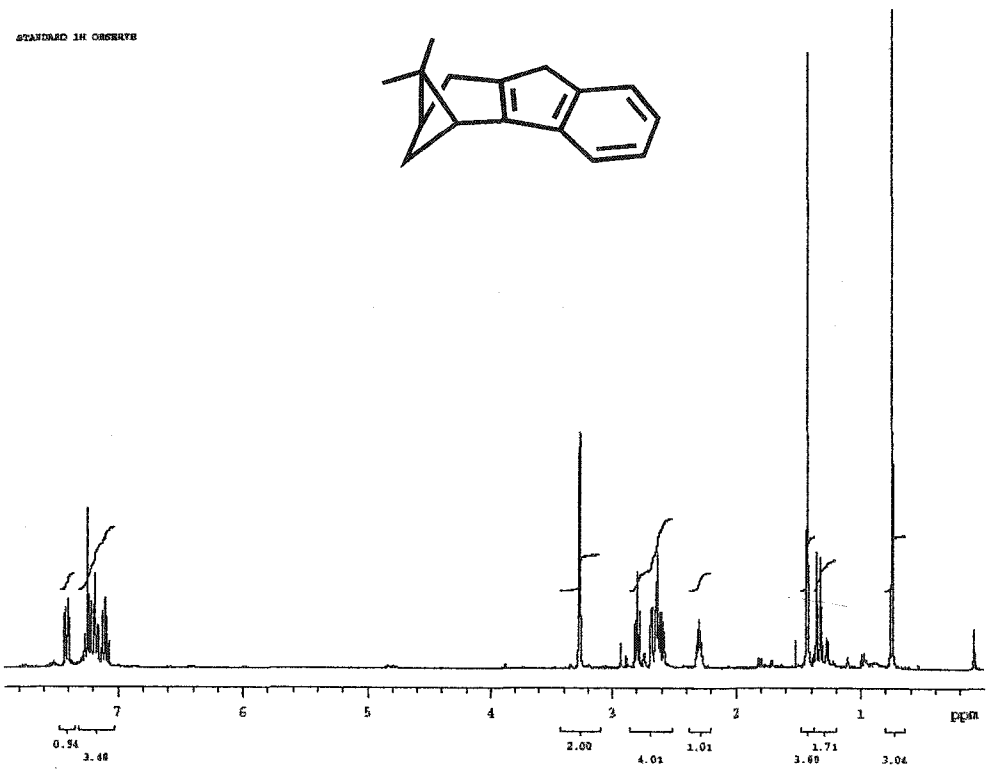
Pinanyl Annelated Indene (5): A dry 100 mL roundbottomed Schlenk flask was charged with chromium (II) chloride (0.0118 mol, 1.45 g) and nickel (II) chloride (0.00017 mol, 0.022 g) under inert atmosphere. Dimethylformamide (10 mL), recently distilled from molecular sieves, was added to the flask under argon and the dark green solution was vigorously stirred. In a dry 25 mL flask, 2-(2-bromobenzyl)-nopinone **11** (0.00407 mol, 1.25 g) was placed under argon, then diluted in distilled dimethylformamide (4 mL) and transferred via syringe to the metal salt solution. The solution was left stirring in 145 °C oil bath for 80 h under argon, then cooled and quenched with water and extracted with copious amounts of dichloromethane, which were combined and washed with water and brine, dried with magnesium sulfate, and concentrated under vacuum to a crude yellow oil (830 mg). A short chromatography column (silica gel, 3:1 CH_2Cl_2/PE) was used to isolate pure pinanyl annelated indene **5** (0.0015 mol, 320 mg, 37% yield) as a yellow oil that congeals over time, and 120 mg of a dimeric alcohol side product, also a yellow oil. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **5** was greater than 95% pure.

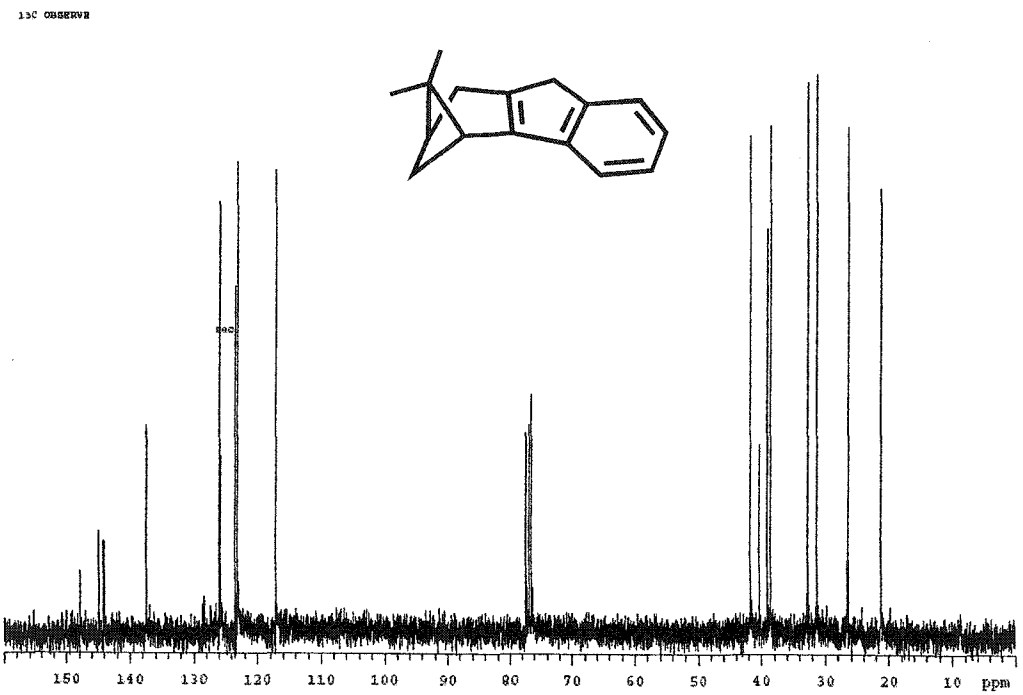
MS (EI, 70 eV, rel %) 210 (100, M^+), 195 (8), 167(13), 165 (10).

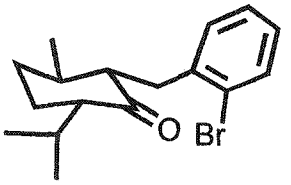
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J=7.5 Hz, 1H), 7.22 (dd, J=7.5, 7.5 Hz, 1H), 7.15 (d, J=7.5 Hz, 1H), 7.07 (dd, J= 7.5, 7.5 Hz, 1H), 3.29 (d, J=23.0 Hz,

1H), 3.24 (d, J=23.0 Hz, 1H), 2.77 (dd, J=5.5, 5.5 Hz, 1H), 2.69 (dd, J=18.0, 3.0 Hz, 1H), 2.62 (dd, J=18.0, 3.0 Hz, 1H), 2.61 (ddd, J=9.0, 5.5, 5.5 Hz, 1H), 2.29 (dddd, J=3.0, 3.0, 5.5, 5.5 Hz, 1H), 1.42 (s, 3H), 1.33 (d, J=9.0 Hz, 1H), 0.72 (s, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 148.2(C), 145.2(C), 144.4(C), 137.8(C), 126.2(CH), 123.8(CH), 123.5(CH), 117.4(CH), 42.0(CH), 40.7(C), 39.43(CH), 38.9(CH_2), 33.1(CH_2), 31.6(CH_2), 26.8(CH_3), 21.6(CH_3).


STANDARD 1H OBSERVE
7
6
5
4
3
2
1
ppm
0.94
3.46
2.00
4.01
1.01
1.71
3.60
3.04


13C OBSERVE
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



References: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448. Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

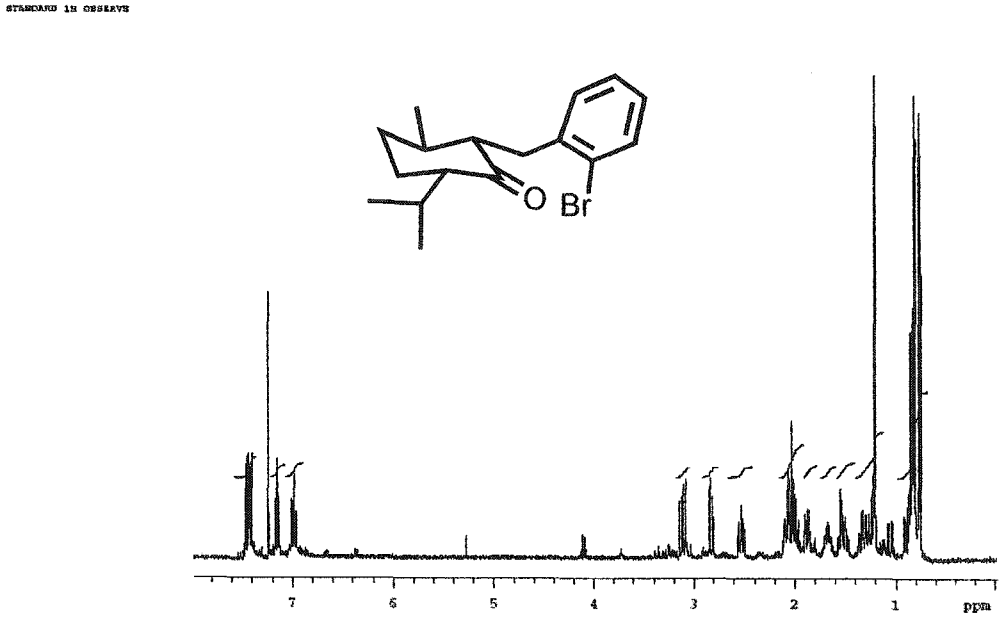
2-(2-Bromobenzyl)-menthone (12): Distilled tetrahydrofuran (100 mL) was added to a dry 250 mL flask under nitrogen containing distilled diisopropylamine (0.043 mol, 6.0 mL). The solution was cooled to -78 °C with a dry ice/acetone bath, then *n*-butyllithium (0.040 mol, 20 mL, 2.0 M in hexane) was added dropwise via syringe. The mixture was allowed to warm to 0 °C over 30 min, then was returned to -78 °C while (-)-menthone (0.034 mol, 5.8 mL) was added dropwise via syringe. The solution was warmed to 0 °C while stirring for 2 h, then a solution of 2-bromobenzylbromide (0.056 mol, 14.0 g) in distilled tetrahydrofuran (15 mL) was rapidly added via syringe to the enolate solution. After stirring under nitrogen overnight, the mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with sodium sulfate and concentrated under vacuum to a crude weight of 14.0 g colorless oil. Column chromatography (silica gel, 2 eq. petroleum ether: 1eq. CH_2Cl_2) was used to isolate the product as colorless oil (0.015 mol, 4.7 g) in 43% yield. Inspection of the ^{1}H-NMR spectrum indicated compound **12** was about 90% pure.

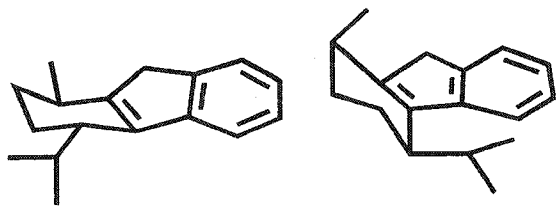
HRMS (TOF ES+, rel.%): 347.0678 (79.5%, $[(M+2)+Na]^+$), 345.0809 (73.2%,

[M+Na]$^+$). [M+Na]$^+$ calcd for $C_{17}H_{23}BrO$, 345.0830.

MS (EI, 70eV, rel%): 323 (13, M^+), 243 (100, loss of Br), 187 (53), 159(15), 131(18), 107(28).

^{1}H-NMR (400 MHz, CDCl3) δ: 7.45(d, J=7.5 Hz, 1H), 7.42(d, J=7.5 Hz, 1H), 7.15(dd, J=7.5, 7.5 Hz, 1H), 6.98(dd, J=7.5, 7.5 Hz, 1H), 3.11(dd, J=13.5, 9.5 Hz, 1H), 2.83(dd, J=13.5, 3.0 Hz, 1H), 2.52 (ddd, J=3.0, 9.5, 12.0 Hz, 1H), 2.08(m, 1H), 2.04(m, 1H), 2.00(dsept, J=6.5, 6.5 Hz, 1H), 1.88(dddd, J=5.5, 5.5, 5.5, 13.5 Hz, 1H), 1.67 (dddq, J= 12.0, 11.5, 4.0, 7.0 Hz, 1H), 1.52(dddd, J=13.0, 12.0, 12.0, 4.0 Hz, 1H), 1.31(dddd, J= 13.0, 11.5, 11.5, 4.0 Hz, 1H), 1.21(d, J=7.0 Hz, 3H), 0.81(d, J=6.5 Hz, 3H), 0.76(d, J=6.5 Hz, 3H).





References: Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445-7448. Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907-2909.

Menthyl Annelated Indenes (6a and 6b): A dry 100 mL roundbottomed Schlenk flask was charged with chromium (II) chloride (0.0179 mol, 2.20 g) and nickel (II) chloride (0.00026 mol, 0.036 g) under inert atmosphere. Dimethylformamide (40 mL), recently distilled from molecular sieves, was added to the flask under argon and the dark green solution was vigorously stirred. In a dry 25 mL flask, 2-(2-bromobenzyl)-menthone **12** (0.00619 mol, 2.00 g) was placed under argon, then diluted in distilled dimethylformamide (15 mL) and transferred via syringe to the metal salt solution. The solution was left stirring in a 125 °C oil bath for 16 h under argon, then cooled and quenched with 6 N HCl (neutral quench results in a mixture of both menthyl annelated indanol and menthyl annelated indene isomers). After a few minutes to allow for acid dehydration, the mixture was extracted with copious amounts of dichloromethane and the organic extracts were washed generously with water and brine, then dried with sodium sulfate and concentrated under vacuum to a crude yellow oil. The resultant 1:1 diastereomeric mixture of indenes was improved to approximately 2:1 upon stirring at room temperature in chloroform with catalytic para-toluenesulfonic acid. After washing with saturated aqueous sodium bicarbonate, and drying with sodium sulfate, the chloroform was removed under vacuum and the mixture of diastereomers was

isolated as a colorless oil (0.0055 mol, 1.24 g, 89% yield). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compounds **6a/6b** were greater than 90% pure.

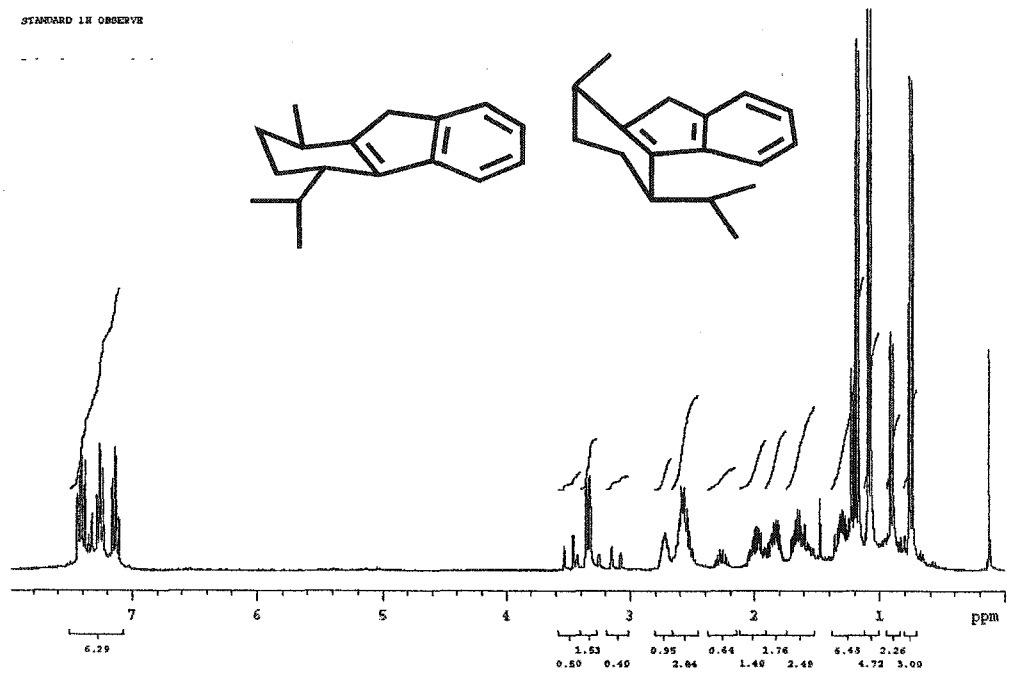
Diastereomeric mixture: IR (thin film): 3045, 3000, 2940, 1595, 1450.

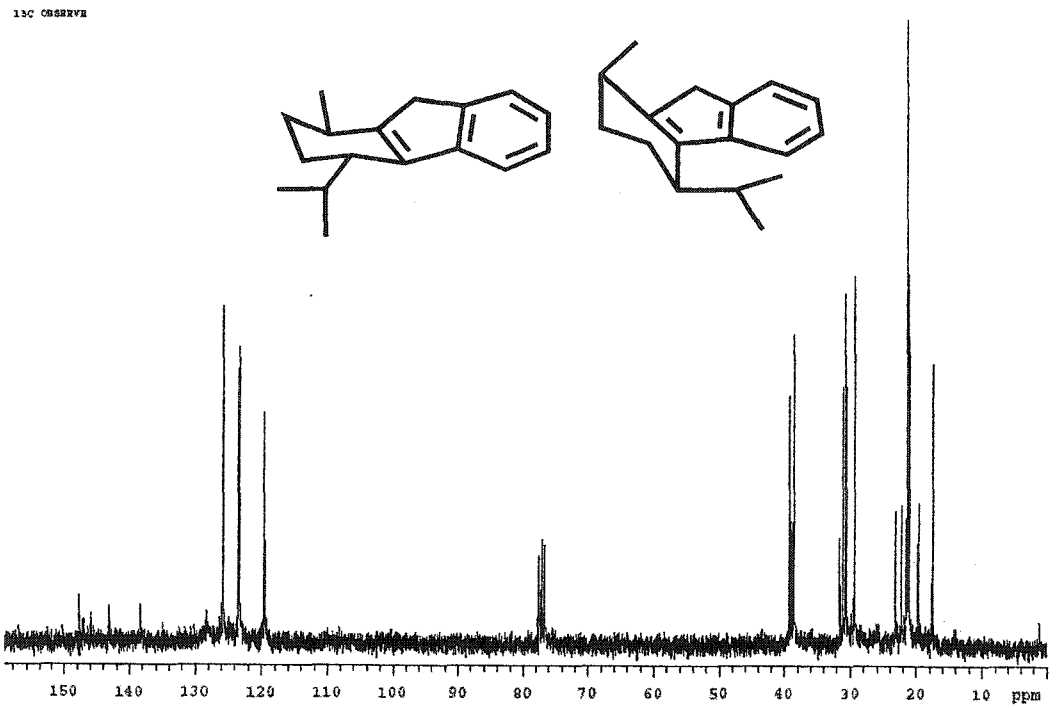
MS (EI, 70 eV, rel %): 226 (100, M^{+}), 211 (14), 183 (70), 167 (11), 155 (22), 141 (23).

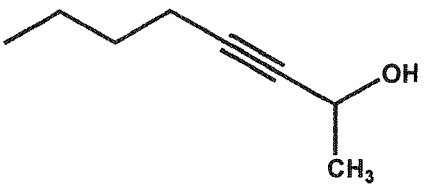
(major isomer) ^{1}H-NMR (300 MHz, $CDCl_3$) δ : 7.40(d, J=7.5 Hz, 1H), 7.36(d, J=7.5 Hz, 1H), 7.22(dd, J=7.5, 7.5 Hz, 1H), 7.10(dd, J=7.5, 7.5 Hz, 1H), 3.35(dd, J=3.0, 23.0 Hz, 1H), 3.28(d, J=23.0 Hz, 1H), 2.69(m, 1H), 2.55(m, 1H), 2.53(m, 1H), 1.96 (m, 1H), 1.80(m, 1H), 1.64(m, 1H), 1.28 (m, 1H), 1.16(d, J=7.0 Hz, 3H), 1.06(d, J=7.0 Hz, 3H), 0.72(d, J=7.0 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ : 147.9(C),146.2(C), 143.4(C), 138.5(C), 126.0(CH), 123.6(CH), 123.5(CH), 119.9(CH), 39.5(CH), 38.8(CH_2), 31.3(CH), 30.9(CH_2), 29.7(CH), 21.7(CH_3), 21.7(CH_2), 21.4(CH_3), 17.9(CH_3).

(minor isomer) ^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ : 147.9 (C), 147.3(C), 143.4(C), 138.5(C), 126.0(CH), 123.6(CH),123.4(CH), 119.7(CH), 39.3(CH_2), 39.0(CH), 31.8(CH), 31.0(CH), 29.7(CH_2), 23.4(CH_2), 22.5(CH_3), 20.0(CH_3), 17.9(CH_3).


STANDARD 1H OBSERVE
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13C OBSERVE
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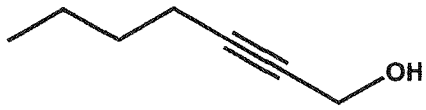


Reference: Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28-29.

Oct-3-yn-2-ol (28): Distilled tetrahydrofuran (70 mL) and 1-hexyne (0.050 mol, 5.7 mL) were added to a dry 250 mL flask under nitrogen. The solution was cooled to -78 °C with an acetone/dry ice bath, then *n*-butyllithium (0.050 mol, 22 mL, 2.25 M in hexane) was added dropwise. After 10 min, freshly distilled acetaldehyde (0.050 mol, 2.8 mL) was added and the solution was left stirring at -78 °C for 20 min, before being quenched with saturated aqueous ammonium chloride. The organic and aqueous phases were separated and the aqueous phase was extracted with three portions of diethyl ether. The combined organic extracts were washed with water and dried with magnesium sulfate, then concentrated under vacuum. The product **28**, a yellow oil, was obtained in quantitative yield (0.050 mol, 6.3 g). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **28** was about 80% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.42 (tq, J=6.5, 2.0 Hz, 1H), 2.80 (br s, 1H), 2.12 (dt, J=7.0, 2.0 Hz, 2H), 1.50-1.20 (m, 4H), 1.34 (d, J=6.5 Hz, 3H), 0.83 (t, J=7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 84.2 (C), 82.2 (C), 58.2 (CH), 30.7 (CH_2), 24.6 (CH_3), 21.8 (CH_2), 18.3 (CH_2), 13.5 (CH_3).



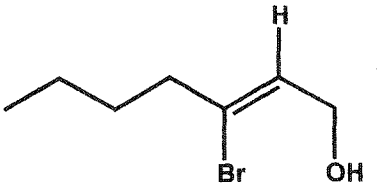
Reference: Zwierzak, A.; Tamassy, B. *Synth. Commun.* **1996**, *19*, 3593-3600.

Hept-2-yn-1-ol (29): In a dry 500 mL roundbottomed flask with reflux condenser attached, 1-hexyne (0.150 mol, 12.3 g) was flushed with nitrogen and distilled tetrahydrofuran (20 mL) was added. Ethyl magnesium chloride, or alternatively propyl magnesium chloride, (0.165 mol, 82.5 mL, 2.0 M in THF) was added via syringe which caused the rapid evolution of gas and reflux. The solution was heated for about 2 h until gas was no longer being evolved, then dry paraformaldehyde (0.195 mol, 5.85 g) which had been dried under vacuum with phosphorus pentoxide, was added in tetrahydrofuran (20 mL) and refluxing was continued for several hours. The clear yellow solution that resulted was neutralized with 1.0 M HCl and extracted with 3 portions of diethyl ether. The combined organic extracts were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum. The product **29** was isolated, after removal of 1-hexyne by vacuum, as a colorless oil (0.131 mol, 14.7 g) in 88% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **29** was about 80% pure. Vacuum distillation increased the purity to greater than 95%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.14 (m, 2H), 3.02 (m, 1H), 2.12 (ddt, J=9.0, 7.0, 2.5, 2.5 Hz, 2H), 1.25-1.46 (m, 4H), 1.82 (t, J=7.0 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 85.9 (C), 78.2 (C), 50.8 (CH_2), 30.6 (CH_2), 21.8 (CH_2), 18.3 (CH_2), 13.5 (CH_3).

Compound **30**: Listed following compound **31**



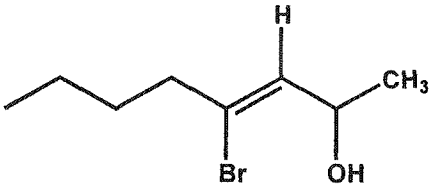
(*Z*)-3-Bromohept-2-en-1-ol (31): In a dry 250 mL roundbottomed flask, lithium aluminum hydride (0.045 mol, 10.7g) was flushed with nitrogen and distilled tetrahydrofuran (45 mL) was added via syringe. The slurry was cooled to 0 °C in a wet ice bath, then hept-2-yn-1-ol **29** (0.030 mol, 3.36 g) was added slowly via syringe causing rapid evolution of hydrogen gas. The slurry was left stirring at room temperature over 72 h. N-bromosuccinimide (0.060 mol, 10.7 g), which had been recrystallized from water and fully dried with phosphorous pentoxide or calcium chloride under vacuum, was flushed with nitrogen in a dry 250 mL flask then dissolved in distilled tetrahydrofuran (100 mL) in a wet ice bath (0°C) or an acetone/wet ice bath (-10 °C) . When the tetrahydrofuran was added at room temperature to the N-bromosuccinimide, *a highly hazardous and exothermic process occurred*; consequently, a lower temperature of 0 °C or -10 °C is very necessary. This solution was added to the lithium aluminum hydride slurry at 0 °C producing a brown mixture. After stirring for 1 h, the brown mixture was quenched and filtered. The aqueous phase was extracted with three portions of diethyl ether and the combined organic phases were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum to a crude orange oil (5.3 g). The oil was passed through a plug of silica gel with dichloromethane to isolate product **31** as an orange oil in 86 % yield (0.026 mol,

5.0 g). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **31** was about 80% pure.

MS (EI, 70 eV, rel %): 193 (4, [(M-H^{+})+2]), 191 (4, M-H^{+}), 177 (7), 175 (7), 151 (5), 149 (5), 113 (5, loss of Br), 95 (100, loss of Br and OH), 67 (87).

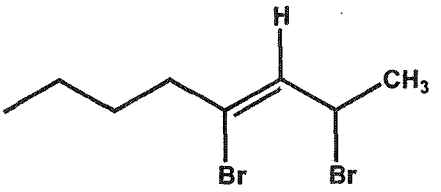
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.88 (tt, J=1.0, 6.0 Hz, 1H), 4.22 (dt, J=1.0, 6.0 Hz, 2H), 2.41 (dtt, J=1.0, 1.0, 7.5 Hz, 2H), 2.28 (br s, 1H), 1.51 (m, 2H), 1.28 (m, 2H), 0.88 (t, J=7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 130.0 (C), 127.3 (CH), 62.3 (CH_2), 41.2 (CH_2), 30.1 (CH_2), 21.6 (CH_2), 13.8 (CH_3).



(Z)-4-Bromooct-3-en-2-ol (30): This compound was prepared from compound **28** with the procedural method described for (*Z*)-3-Bromohept-2-en-1-ol (**31**). Compound **30** was isolated as a pure orange oil in 60% yield. Inspection of the ^{1}H-NMR spectrum indicated compound **30** was about 90% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.72 (dt, J=7.5, 1.0, 1.0 Hz, 1H), 4.64 (dq, J=6.5, 6.5, 6.5, 7.5 Hz, 1H), 2.41 (dt, J=1.0, 7.0 Hz, 2H), 1.52 (m, 2H), 1.38-1.18 (m, 2H), 1.27 (d, J=6.5 Hz, 3H), 0.90 (t, J=7.5 Hz, 3H), 0.44 (br s, 1H).

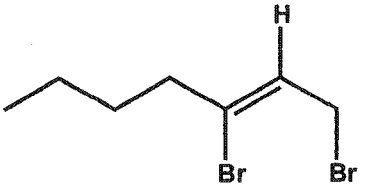


(*Z*)-2,4-Dibromo-oct-3-ene (32): In a dry 25 mL roundbottomed flask (*Z*)-4-bromo-oct-3-en-2-ol **30** (0.0024 mol, 0.50 g) and carbon tetrabromide (0.0034 mol, 1.1 g) were combined and flushed with nitrogen. Distilled dichloromethane (5 mL) was added via syringe and the solution was cooled in an ice bath to 0 °C. In a 10 mL flask, triphenylphosphine (0.0067 mol, 1.8 g) was flushed with nitrogen and dissolved in distilled dichloromethane (2 mL), then transferred via syringe to the solution at 0 °C, causing the solution to immediately develop a brown color. After stirring at room temperature for 4 h, the mixture, which now contained a white precipitate, was quenched with water, filtered and concentrated under vacuum. Petroleum ether was added and solids were again filtered off, then the organic phase was separated from the aqueous phase and the latter was extracted with three portions of petroleum ether. The combined organic extracts were washed with water and brine, dried with magnesium sulfate and concentrated under vacuum. After purification by passing through a small plug of silica gel with petroleum ether, the product **32** was isolated as a yellow oil (0.0020 mol, 0.55g) in 85% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **32** was about 80% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.90 (dt, J=1.0, 1.0, 9.5 Hz, 1H), 4.99 (dq, J= 6.5, 6.5, 6.5, 9.5 Hz, 1H), 2.44 (dt, J= 1.0, 7.5, 7.5 Hz, 2H), 1.76 (d, J=6.5 Hz, 3H), 1.54 (m, 2H), 1.31 (m, 2H), 0.91 (t, J= 7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 130.9 (CH), 130.6 (C), 47.5 (CH), 41.0 (CH_2),

30.0 (CH_2), 26.0 (CH_3), 21.5 (CH_2), 13.9 (CH_3).



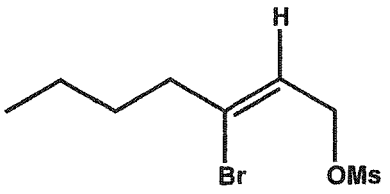
1,3-Dibromohept-2-ene (33):

In a dry 100 mL roundbottomed flask, carbon tetrabromide (0.025 mol, 8.3 g) was flushed with nitrogen and distilled dichloromethane (10 mL) was added via syringe. The solution was cooled to 0 °C with a wet ice bath, then triphenylphosphine (0.050 mol, 13.1 g) in distilled dichloromethane (20 mL) was added dropwise via syringe causing an orange color to develop. The solution was allowed to warm to room temperature over 15 min, then (Z)-3-bromohept-2-en-1-ol **31** (0.018 mol, 3.5 g) in distilled dichloromethane (25 mL) was added dropwise in four portions over 2 hours. The brown mixture was left stirring at room temperature for an additional three hours before it was filtered through a small plug of silica gel with dichloromethane. The solvent was removed from this orange solution by vacuum and solid impurities were removed by trituration with petroleum ether. Upon removal of the petroleum ether by vacuum, the product **33** was isolated as a colorless oil (0.012 mol, 3.0 g) in 65% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **33** was about 80% pure.

MS (EI, 70 eV, rel %): 253 (1), 213 (2), 177 (7), 175 (7), 95 (100), 67 (62).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.96 (tt, J=1.5, 8.0 Hz, 1H), 4.04 (d, J=8.0 Hz, 2H), 2.47 (t, J=7.5 Hz, 2H), 1.53 (m, 2H), 1.29 (m, 2H), 0.89 (t, J=7.0 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 134.7 (C), 124.2 (CH), 41.3 (CH_2), 30.3 (CH_2), 30.0 (CH_2), 21.5 (CH_2), 13.8 (CH_3).

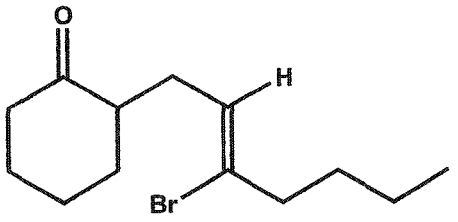


Mesylate of (*Z*)-3-bromohept-2-en-1-ol (34):

In a dry 100 mL roundbottomed flask, triethylamine (0.016 mol, 1.62 g) and (*Z*)-3-bromohept-2-en-1-ol **31** (0.014 mol, 2.70 g) were flushed with nitrogen and distilled dichloromethane (25 mL) was added via syringe. After the solution had been cooled to -10 °C in a wet ice/acetone bath, methanesulfonyl chloride (0.021 mol, 1.63 mL) was added dropwise via syringe. The solution was left stirring overnight under nitrogen. The brown solution was washed with water repeatedly, dried with magnesium sulfate and concentrated under vacuum to a crude brown oil (3.03 g). The oil was passed through a plug of silica gel with dichloromethane to isolate product **34** as an orange oil in 46 % yield (0.0065 mol, 1.55 g). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **34** was about 75% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.92 (br t, J= 6.5, 6.5 Hz, 1H), 4.83 (br d, J=6.5 Hz, 2H), 3.02 (s, 3H), 2.49 (t, J=7.5, 7.5 Hz, 2H), 1.55 (m, 2H), 1.31 (m, 2H), 0.91 (t, J=7.5, 7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 135.6 (C), 121.4 (CH), 69.3 (CH_2), 41.6 (CH_2), 38.0 (CH_3), 30.3 (CH_2), 21.9 (CH_2), 14.2 (CH_3).

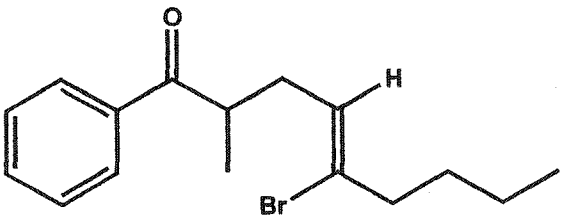


(*Z*)-1-[1-(3-Bromohept-2-enyl)]-cyclohexanone (35): In a dry 25 mL roundbottomed flask, previously distilled diisopropylamine (0.0037 mol, 0.52 g) was flushed with nitrogen and distilled tetrahydrofuran (5 mL) was added via syringe. The flask was cooled to -78 °C with a dry ice/acetone bath and *n*-butyllithium (0.0037 mol, 1.8 mL, 2.1 M in hexane) was added dropwise via syringe. Then, the solution was allowed to warm to room temperature over 30 min, and returned to -78 °C before cyclohexanone (0.0033 mol, 0.34 mL) was added dropwise via syringe. The pale yellow solution was stirred at -78 °C for 1 h then warmed to room temperature for another hour, before the mesylate of (*Z*)-3-bromohept-2-en-1-ol **34** (0.0050 mol, 1.2 g) was added rapidly via syringe and the solution continued stirring at room temperature overnight. The mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum. Column chromatography (silica gel, dichloromethane) was used to isolate the product, a colorless oil (0.0018 mol, 0.51 g) in 57% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **35** was about 80% pure.

MS (EI, 70 eV, rel %): 275 (35, M+2), 273 (53, M^{+}), 193 (100, loss of Br), 95 (56).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.65 (ddt, J=7.5, 6.5, 1.5, 1.5 Hz, 1H), 2.45 (m, 1H), 2.39 (m, 1H), 2.38 (t, J=7.5, 7.5 Hz, 2H), 2.30 (m, 1H), 2.20 (m, 1H), 2.05 (m, 2H), 1.84 (m, 1H), 1.64 (m, 2H), 1.49, (m, 2H), 1.47 (m, 1H), 1.38 (m, 1H), 1.27 (m, 2H), 0.88 (t, J=7.5, 7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 212.5 (C), 130.1 (C), 126.3 (CH), 50.5 (CH), 42.4 (CH_2), 41.7 (CH_2), 34.0 (CH_2), 31.8 (CH_2), 30.7 (CH_2), 28.3 (CH_2), 25.4 (CH_2), 21.9 (CH_2), 14.2 (CH_3).

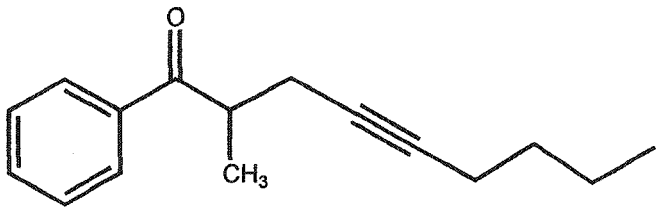


(*Z*)-5-Bromo-2-methyl-1-phenylnon-4-en-1-one (39): In a dry 25 mL roundbottomed flask, previously distilled diisopropylamine (0.0069 mol, 0.70 g) was flushed with nitrogen and distilled tetrahydrofuran (10 mL) was added via syringe. The flask was cooled to -78 °C with a dry ice/acetone bath and *n*-butyllithium (0.0069 mol, 2.8 mL, 2.46 M in hexane) was added dropwise via syringe. Then, the solution was allowed to warm to room temperature over 30 min, and returned to -78 °C before propiophenone (0.0063 mol, 0.85 g) was added dropwise via syringe. The pale yellow solution was stirred at -78 °C for 1 h then warmed to 0 °C for another hour, before (*Z*)-1,3-dibromohept-2-ene **33** (0.0094 mol, 2.4 g) was added rapidly via syringe and the solution was left stirring at room temperature overnight. The mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum to a crude orange oil (2.24g). Column chromatography (silica gel, 2:1 dichloromethane/petroleum ether) was used to isolate the product, a colorless oil (0.00486 mol, 1.53 g) in 77% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **39** was greater than 95% pure.

MS (EI, 70 eV, rel.%): 311 (10, $[M+2]^+$), 309 (10, M^+), 229 (20, loss of Br), 105 (100), 91 (36), 77 (59), 57 (22).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.94 (d, J=7.0 Hz, 2H), 7.53 (dd, J=7.0, 7.0 Hz, 1H), 7.44 (dd, J=7.0, 7.0 Hz, 2H), 5.64 (ddt, J=1.0, 1.0, 7.0, 7.5 Hz, 1H), 3.58 (ddq, J=7.0, 7.0, 7.0, 14.0, 14.0 Hz, 1H), 2.57 (ddd, J=7.0, 7.0, 14.0 Hz, 1H), 2.36 (m, 1H), 2.36 (t, J=7.0 Hz, 2H), 1.45 (tt, J=7.0, 7.0 Hz, 2H), 1.23 (m, 2H), 1.20 (d, J=7.0 Hz, 3H), 0.84 (t, J=7.0 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 203.3 (C), 136.2 (C), 132.9 (CH), 130.4 (C), 128.6 (CH, 2C), 128.3 (CH, 2C), 125.4 (CH), 41.2 (CH_2), 40.0 (CH), 34.8 (CH_2), 30.1 (CH_2), 21.4 (CH_2), 17.1 (CH_3), 13.7 (CH_3).



2-Methyl-1-phenylnon-4-yn-1-one (41):

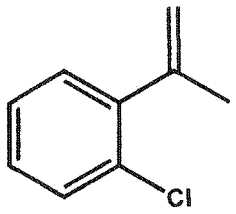
A dry 100 mL roundbottomed Schlenk flask was charged with chromium (II) chloride (0.00076 mol, 0.093 g), nickel (II) chloride (0.00079 mol, 0.098 g), and lithium bromide (0.015 mol, 1.3 g) under inert atmosphere. Dimethylformamide (30 mL), recently distilled from molecular sieves, was added to the flask under argon and the dark green solution was vigorously stirred. In a dry 25 mL flask, (*Z*)-5-bromo-2-methyl-1-phenylnon-4-en-1-one **39** (0.00076 mol, 2.35 g) was placed under argon, then diluted in distilled dimethylformamide (10 mL) and transferred via syringe to the metal salt solution. Under an overpressure of argon, the septum was removed, then 50 mesh manganese powder (0.0152 mol, 0.84 g) and chlorotrimethylsilane (0.015 mol, 1.95 mL) were added rapidly, before the flask was sealed with a glass stopper. The sealed solution was left stirring in 148 °C oil bath for 24 h, then cooled and quenched with water and extracted with copious amounts of dichloromethane, which were combined and washed with water and brine, dried with magnesium sulfate, and concentrated under vacuum to a crude orange oil (0.9 g). Column chromatography (silica gel, dichloromethane) was used to isolate 2-methyl-1-phenylnon-4-yn-1-one **41** (0.0021 mol, 0.48 g) in 28% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **41** was greater than 95% pure.

MS (EI, 70 eV, rel.%): 229 ([M+H]$^{+}$, 100), 185 (35), 171 (12), 157 (23), 105 (23),

77 (13).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.94 (d, J=7.0 Hz, 2H), 7.53 (dd, J=7.5, 7.5 Hz, 1H), 7.44 (dd, J=7.0, 7.5 Hz, 2H), 3.61 (ddq, J=6.5, 6.5, 6.5, 6.5, 8.0 Hz, 1H), 2.55 (ddt, J=16.5, 6.5, 2.0, 2.0 Hz, 1H), 2.33 (ddt, J=16.5, 8.0, 2.5, 2.5 Hz, 1H), 2.07 (tt, J=3.0, 7.0 Hz, 2H), 1.43-1.27 (m, 4H), 1.26 (d, J=6.5 Hz, 3H), 0.83 (t, J=7.0 Hz, 3H).

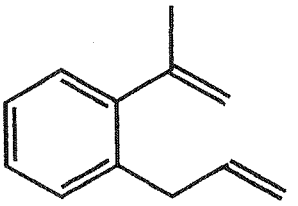
^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 202.9 (C), 136.2 (C), 132.9 (CH), 128.6 (CH, 2C), 128.3 (CH, 2C), 81.9 (C), 77.7 (C), 40.7 (CH), 31.0 (CH_2), 22.8 (CH_2), 21.8 (CH_2), 18.3 (CH_2), 17.3 (CH_3), 13.5 (CH_3).



Reference: Sondheimer, F.; Mechoulam, R. *J. Am. Chem. Soc.* **1957**, *79*, 5029-5033.

1-Chloro-2-(1-methylethenyl)-benzene (71): Distilled diethyl ether (150 mL) was added to methyltriphenylphosphonium bromide (0.030 mol, 10.7 g) in a dry 250 mL flask under nitrogen. The slurry was stirred at 0 °C in an ice bath while *n*-butyllithium (0.027 mol, 12 mL, 2.25 M in hexane) was added dropwise. The light orange solution that resulted was allowed to stir at room temperature for 45 min, then 2'-chloroacetophenone (0.030 mol, 4.6 g) was added via syringe causing a white powder to form. After stirring overnight, the reaction was quenched with water and extracted with three portions of diethyl ether. The combined organic extracts were washed with water, 0.5 M HCl, and water again, then dried with magnesium sulfate and concentrated under vacuum. Column chromatography (silica gel, petroleum ether) was used to isolate the product **71**, a yellow oil (0.0189 mol, 2.88g) in 70% yield. Inspection of the ^{1}H-NMR spectrum indicated compound **71** was greater than 95% pure.

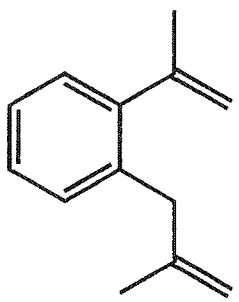
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33 (m, 1H), 7.15-7.20 (m, 3H), 5.21 (dq, J=1.5, 1.5, 1.5, 1.5 Hz, 1H), 4.95 (br d, J=1.5 Hz, 1H), 2.09 (br s, 3H).



Reference: Ahluwali, V. K. *Chemical Abstracts* **63**, 14747.

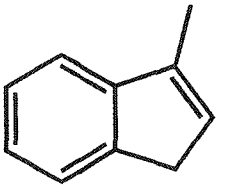
1-(1-Methylethenyl)-2-(2-propenyl)-benzene (73) or 1-(1-Methylethenyl)-2-(2-methyl-2-propenyl)-benzene (72): Crushed magnesium turnings (0.060 mol, 1.46g) were placed in a dry 150 mL flask attached to a condenser. Distilled tetrahydrofuran (5 mL) was added, followed by 0.3 mL of 1,2-dibromoethane. When the visible evolution of ethene gas subsided, additional tetrahydrofuran (20 mL) was added, and brought to a reflux. After stirring at reflux for 60 min, 1-chloro-2-(1-methylethenyl)-benzene **71** (0.017 mol, 2.6 g) was added via syringe and refluxing was continued for 24 h. The dark solution was cooled and an aliquot was removed and exothermically quenched in water, confirming the formation of the Grignard reagent. For the synthesis of compound **73**, a 100 mL flask under nitrogen was charged with 3-chloropropene (0.017 mol, 1.30 g) and tetrahydrofuran (5 mL), then approximately half of the dark solution of Grignard reagent (~0.008 mol) was transfered into the flask via syringe. After stirring for 20 h at room temperature, the solution was quenched with water and extracted with three portions of petroleum ether. The combined organic extracts were washed with water and dried with magnesium sulfate then concentrated under vacuum to obtain the product **73** as colorless oil (0.0042 mol, 0.67 g, 53% yield). Inspection of the ^{1}H-NMR spectrum indicated compound **73** was greater than 95% pure. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.18-7.20 (m, 2H), 7.15 (m, 1H), 7.11 (dt, J=1.5,

1.5, 7.0 Hz, 1H), 5.94 (ddt, J=6.5, 6.5, 10.0, 16.5 Hz, 1H), 5.17 (dq, J=1.5, 1.5, 1.5, 1.5 Hz, 1H), 5.03 (ddt, J=1.5, 1.5, 1.5, 10.0 Hz, 1H), 5.00 (ddt, J=1.5, 1.5, 1.5, 16.5 Hz, 1H), 4.83 (d, J=1.5 Hz, 1H), 3.40 (dt, J=1.5, 1.5, 6.5 Hz, 2H), 2.02 (br s, 3H).



For the synthesis of compound **72**, the same procedure was followed and using the other half of the Grignard reagent, but the 100 mL flask was charged with 3-chloro-2-methylpropene (0.017 mol, 1.54 g) instead. Following workup, the product **72**, a colorless oil, was obtained (0.0069 mol, 1.20 g) in 86% yield. Inspection of the ^{1}H-NMR spectrum indicated compound 72 was greater than 95% pure.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.09-7.18 (m, 4H), 5.15 (dq, J=1.5, 1.5, 1.5, 2.0 Hz, 1H), 4.82 (br d, J=1.5 Hz, 1H), 4.80 (br d, J=1.5 Hz, 1H), 4.55 (br s, 1H), 3.33 (br s, 2H), 2.00 (s, 3H), 1.67 (s, 3H).



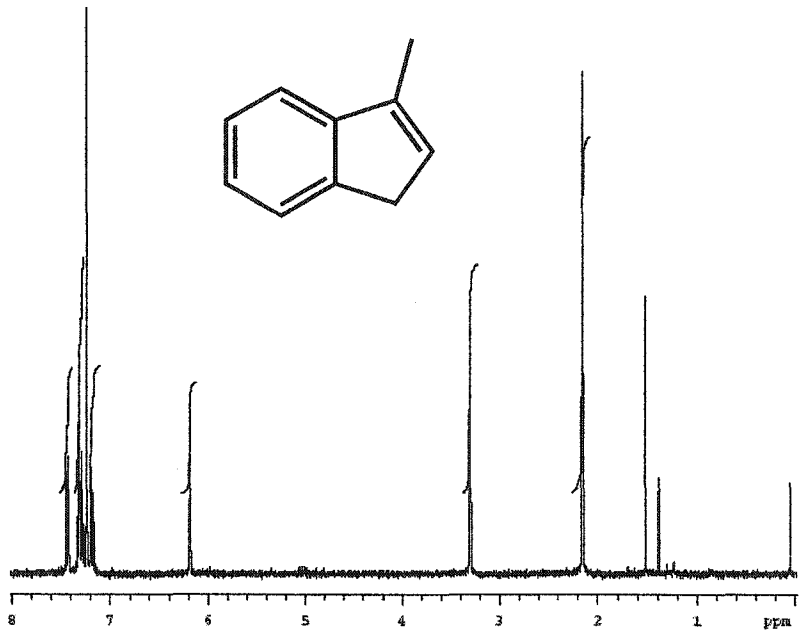
Reference: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318.

1H-3-Methylindene (75): A dry 25 mL Schlenk flask was charged with 2,6-Diisopropylphenylimidoneophylidene molybdenum (IV) bis(hexafluoro-*t*-butoxide, also known as Schrock's Catalyst, **42** (0.020 mmol, 0.012 g) under inert atmosphere. In a dry 25 mL flask, 1-(1-methylethenyl)-2-(2-propenyl)-benzene **73** (100 μL) was placed under argon, then distilled benzene (4 mL) were added via syringe. The solution was degassed, then transferred via syringe to the Schlenk flask. The evolution of ethene gas was immediately observed from the brown solution, which was left stirring under argon flow at 70 °C for 24 h. The brown solution was passed through silica gel with petroleum ether until clear, then concentrated under vacuum to a colorless oil (0.00064 mol, 0.083 g). The ^{1}H-NMR spectrum showed complete conversion to product **75** and indicated that the product was greater than 95% pure.

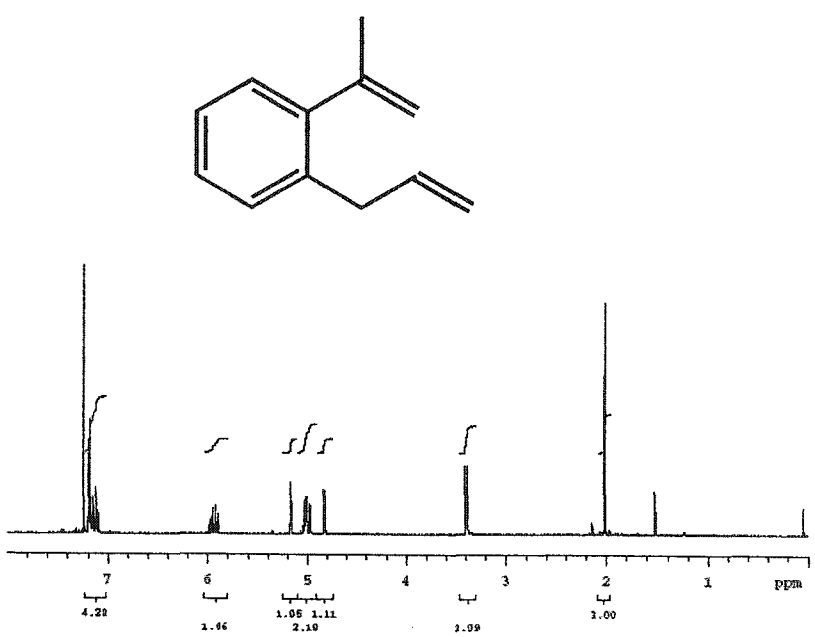
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44 (d, J=7.5 Hz, 1H), 7.33 (d, J=7.5 Hz, 1H), 7.29 (dd, J=7.5, 7.5 Hz, 1H), 7.19 (dd, J=7.5, 7.5 Hz, 1H), 6.19 (m, 1H), 3.30 (m, 2H), 2.15 (m, 3H).

When the procedure described above was used with compound **72**, the ^{1}H-NMR spectrum showed no reaction had occurred; none of the expected product 1H-2,3-dimethylindene **74** was formed and starting material **72** was recovered.

STANDARD 1H OBSERVE

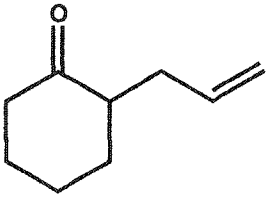


STANDARD 1H OBSERVE



Compound **76**: Listed following compound **79**

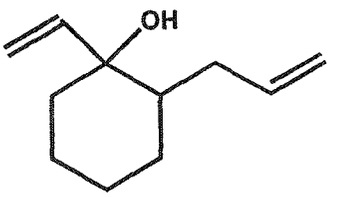
Compound **77**: Listed following compound **86**



Reference: Shaughnessy, K. H.; Waymouth, R. M. *Organometallics* **1998**, *17* (26), 5728-5745.

2-(Prop-2-en-1-yl)-cyclohexan-1-one (78): In a dry 250 mL roundbottomed flask, previously distilled diisopropylamine (0.088 mol, 8.9 g) was flushed with nitrogen and distilled tetrahydrofuran (75 mL) was added via syringe. The flask was cooled to -78 °C with a dry ice/acetone bath and *n*-butyllithium (0.084 mol, 39.3 mL, 2.14 M in hexane) was added dropwise via syringe. The solution was allowed to warm to room temperature over 30 min, and returned to -78 °C before cyclohexanone (0.070 mol, 6.87 g) was added dropwise via syringe. The pale yellow solution was stirred at -78 °C for 1 h then warmed to room temperature for another hour, before allyl bromide (0.120 mol, 14.5 g) was added rapidly via syringe and the solution continued stirring at room temperature overnight. The mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum. Solid side product (0.0030 mol, 0.41g, 4%) from O-alkylation was filtered away from the C-alkylation product, an orange oil (0.066 mol, 9.1 g, 94 % yield). The product **78** may be further purified by distillation or

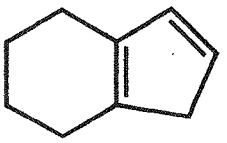
column chromatography (2:1 petroleum ether/dichloromethane) to a colorless oil. Inspection of the ^{1}H-NMR spectrum indicated compound **78** was about 80% pure. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.75 (m, 1H), 5.00 (m, 2H), 2.52 (m, 1H), 2.42-2.23 (m, 3H), 2.15-1.90 (m, 3H), 1.85 (m, 1H), 1.73-1.60 (m, 2H), 1.34 (m, 1H).



1-Ethenyl-2-(prop-2-en-1-yl)-cyclohexan-1-ol (79): In a dry 50 mL roundbottomed flask, 2-(prop-2-en-1-yl)-cyclohexan-1-one **78** (0.01 mol, 1.38 g) was flushed with nitrogen and distilled diethyl ether (30 mL) was added via syringe. While the solution stirred at room temperature, vinyl magnesium bromide (0.020 mol, 20 mL, 1.0 M in tetrahydrofuran) was added dropwise via syringe. After stirring overnight, the solution was quenched with 0.5 M HCl and extracted with three portions of diethyl ether. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and water, then dried with magnesium sulfate and concentrated under vacuum. Column chromatography (silica gel, dichloromethane) was used to isolate the product **79**, a pale yellow oil (0.0018 mol, 0.307 g) in 18% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **79** was about 90% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.83 (dd, J=17.0, 10.5 Hz, 1H), 5.73 (ddt, J=16.5, 8.5, 5.5, 5.5 Hz, 1H), 5.23 (dd, J=17.0, 1.5 Hz, 1H), 5.07 (dd, J=10.5, 1.5 Hz, 1H), 4.96 (br dd, J=16.5, 1.5, 1H),4.94 (br dt, J=8.5, 5.5, 5.5, 1H), 2.22 (m, 1H), 1.10-1.85 (m, 10H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 145.9 (CH), 137.8 (CH), 115.7 (CH_2), 111.7 (CH_2), 74.7 (C), 43.9(CH), 39.1 (CH_2), 34.7 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 21.5 (CH_2).



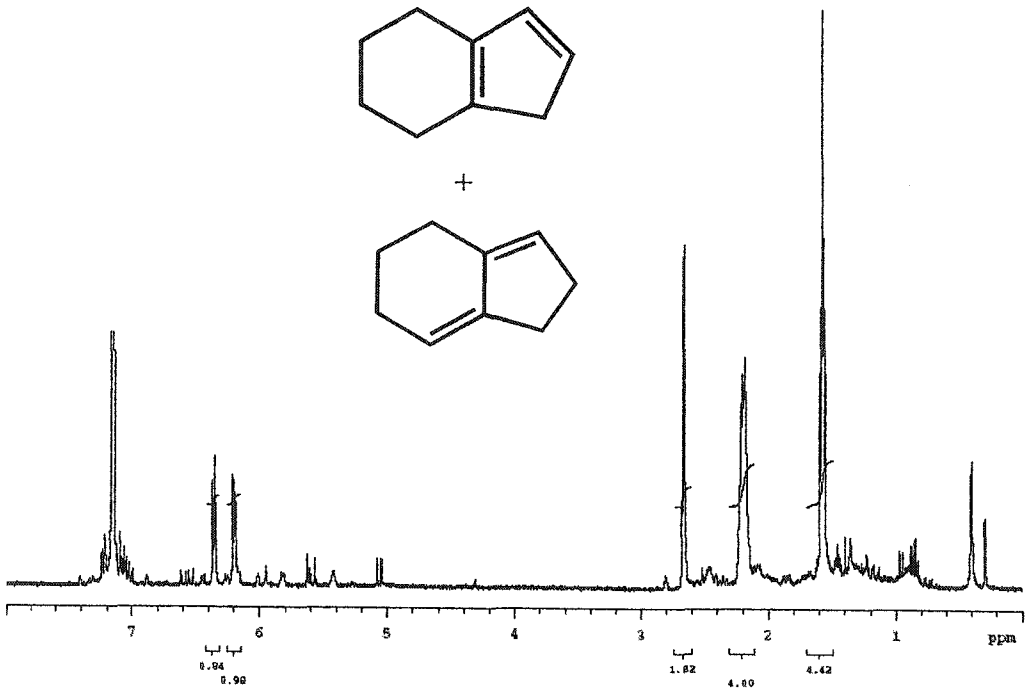
1H-4,4,7,7-Tetrahydroindene (76): A dry 25 mL Schlenk flask was charged with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-ylidene][benzylidene]ruthenium(IV) dichloride, also known as Grubb's II Catalyst, **44** (0.00003 mol, 0.026g) and 2 mL of distilled benzene-d_6 solvent under inert atmosphere. In a dry 25 mL flask, 1-ethenyl-2-(prop-2-en-1-yl)-cyclohexan-1-ol 79 (0.0006 mol, 100 mg) was placed under argon. The purple benzene-d_6/catalyst solution was transferred via cannula to the 25 mL flask, then returned to the Schlenk flask after mixing with the 1-ethenyl-2-(prop-2-en-1-yl)-cyclohexan-1-ol **79**. The mixture was stirred in a 60 °C oil bath for 18 h with a bubbler attached to release ethene gas. The solution was passed through Celite filter agent and silica gel with benzene-d_6 and NMR spectral data was collected on the fractions. After NMR spectral characterization, the fractions containing product **76** were combined. After the solvent was removed by vacuum, 14 mg of pale yellow oil were isolated (0.00012 mol, 19% yield).

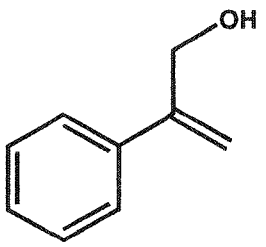
In a subsequent experiment, an equimolar amount of *p*-xylene to 1-ethenyl-2-(prop-2-en-1-yl)-cyclohexan-1-ol **79** was included in the reaction mixture and the reaction was run in a 68 °C oil bath. The ^{1}H-NMR spectrum of the mixture, after the same workup procedure was performed, revealed a mere 10% yield by comparison of the integrations of the product signals with the *p*-xylene methyl signal integration. In the absence of starting material after a successful reaction run (exposure to air or loss of solvent during the reaction time occasionally

resulted in recovered starting material), it seemed probable that the high volatility of the product was causing the apparently low yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **76** was about 75% pure, with the major impurity being rearranged s-*trans* diene.

^{1}H-NMR (300 MHz, C_6D_6) δ: 6.36 (dt, J=1.5, 1.5, 5.5 Hz, 1H), 6.20 (br d, J=5.5 Hz, 1H), 2.67 (ddt, J=1.0, 1.5, 2.5, 2.5 Hz, 2H), 2.20 (m, 4H), 1.58 (m, 4H).

^{13}C-NMR (300 MHz, C_6D_6) δ: 138.7, 134.8, 129.9, 128.6, 43.7, 25.8, 24.9, 23.9, 23.7.





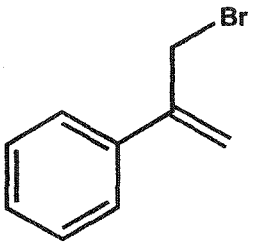
Reference: Organ, M. G.; Murray, A. P. *J. Org. Chem.* **1997**, *62*, 1523-1526.

2-Phenylprop-2-en-1-ol (85): In a dry 250 mL roundbottomed flask, crushed magnesium turnings (0.072 mol, 1.75g) were flushed with nitrogen, then distilled tetrahydrofuran (60 mL) and bromobenzene (0.072 mol, 11.31 g) were added via syringe. The flask was placed in a water bath to prevent spontaneous reflux caused by the exothermic reaction. A few hours later, the Grignard reagent had fully formed. At this time, another dry 250 mL flask containing 2-chloro-2-propen-1-ol (0.030 mol, 2.78g) under nitrogen and distilled tetrahydrofuran (35 mL), was chilled to approximately -10 °C with a wet ice/acetone bath before *n*-butyllithium (0.030 mol, 12.2 mL, 2.46 M in hexane) was added dropwise via syringe. The mixture was warmed to room temperature over 15 min. [1,3-Bis(diphenylphosphino)-propane]dichloronickel (II) (0.0015 mol, 0.81g) in distilled tetrahydrofuran (5 mL) was transferred via cannula into this solution from a 25 mL flask under inert atmosphere, and then the Grignard reagent was also transferred via cannula into the solution, which was stirred in a 45 °C oil bath overnight under nitrogen. The solution was cooled to room temperature and quenched with 1.0 M HCl, then extracted with three portions of diethyl ether. The combined organic extracts were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum to a crude orange oil which contained mainly biphenyl and product. Column chromatography (silica gel, 1:3

diethyl ether/dichloromethane) was used to isolate the product **85** as a pale yellow oil (0.022 mol, 2.9 g) in 72% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **85** was about 90% pure.

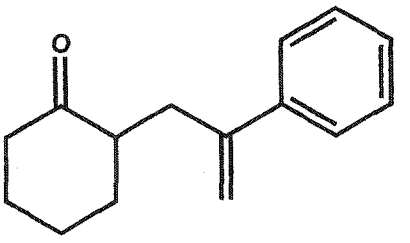
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40-7.25 (m, 5H), 5.41(d, J=1.0 Hz, 1H), 5.29 (dd, J=1.0, 2.5 Hz, 1H), 4.44 (d, J=1.0 Hz, 2H), 2.45 (br s., 1H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ:147.1, 138.5, 128.4 (2 C), 127.8, 125.9 (2 C), 112.3, 64.6.



1-Bromo-2-phenylprop-2-ene (82): A dry 100 mL roundbottomed flask containing 2-phenylprop-2-en-1-ol **85** (0.017 mol, 2.3 g) and carbon tetrabromide (0.027 mol, 9.0 g) was flushed with nitrogen. Distilled dichloromethane (35 mL) was added via syringe and the solution was cooled to 0 °C in a wet ice bath. In another flask, triphenylphosphine (0.053 mol, 13.9 g) was flushed with nitrogen and dissolved in distilled dichloromethane (20 mL), then transferred via cannula into the cooled solution causing an immediate brown color to develop. After stirring at room temperature for 5 h, the mixture, which now contained a white precipitate, was quenched with water, filtered, and concentrated under vacuum. Petroleum ether was added and solids were again filtered off, then the organic phase was separated from the aqueous phase and the latter was extracted with three portions of petroleum ether. The combined organic extracts were washed with water and brine, dried with magnesium sulfate and concentrated under vacuum. After purification by passing through a small plug of silica gel with petroleum ether, the product **82** was isolated as an orange oil (0.013 mol, 2.53 g) in 77% yield. Inspection of the ^{1}H-NMR spectrum indicated compound **82** was about 80% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.69-7.29 (m, 5H), 5.54 (s, 1H), 5.48 (d, J=0.5 Hz, 1H), 4.37 (d, J=0.5 Hz, 2H).

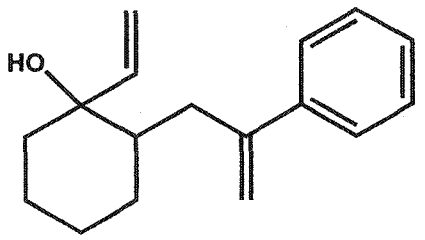


2-(2-Phenylprop-2-en-1-yl)-cyclohexan-1-one (83): In dry 100 mL roundbottomed flask, previously distilled diisopropylamine (0.0125 mol, 1.26 g) was flushed with nitrogen and distilled tetrahydrofuran (10 mL) was added via syringe. The flask was cooled to -78 °C with a dry ice/acetone bath and *n*-butyllithium (0.010 mol, 4.1 mL, 2.46 M in hexane) was added dropwise via syringe. Then, the solution was allowed to warm to room temperature over 30 min, and returned to -78 °C before cyclohexanone (0.0083 mol, 0.81g) in distilled tetrahydrofuran (5 mL) was added dropwise via syringe. The solution was stirred at room temperature for 2 h, then 1-bromo-2-phenylprop-2-ene **82** (0.0087 mol, 1.71 g) in tetrahydrofuran (3 mL) was added rapidly via syringe. The orange solution was left stirring at room temperature overnight. The mixture was quenched with saturated aqueous sodium bicarbonate. The aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum. After column chromatography (silica gel, 3:1 petroleum ether/diethyl ether), product **83** was isolated as a yellow oil in 23% yield (0.0019 mol, 0.400 g). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **83** was about 90% pure.

MS (EI, 70 eV, rel.%): 215 (100, M+1), 214 (15, M^{+}), 197 (39), 179 (21), 149 (7), 91 (4).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.44-7.25 (m, 5H), 5.35 (dd, J=0.5, 1.0 Hz, 1H), 5.10 (br dd, J=0.5, 1.0 Hz, 1H), 3.32 (br d, J= 12.5 Hz, 1H), 2.44 (ddt, J=13.5, 6.5, 6.5, 2.0 Hz, 1H), 2.37 (m, 1H), 2.30 (dt, J=13.5, 13.5, 4.5 Hz, 1H), 2.28 (ddd, J= 13.5, 13.5, 4.5 Hz, 1H), 2.15 (m, 1H), 2.08 (m, 1H), 1.84 (m, 1H), 1.62 (m, 2H), 1.33 (dddd, J=12.5, 12.5, 12.0, 3.0 Hz, 1H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 212.5 (C), 146.1 (C), 140.4 (C), 128.3 (CH, 2 C), 127.4 (CH), 126.1 (CH, 2 C), 114.3 (CH_2), 48.3 (CH), 41.9 (CH_2), 35.0 (CH_2), 33.1 (CH_2), 27.8 (CH_2), 24.8 (CH_2).



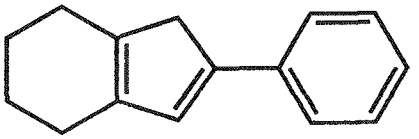
1-Ethenyl-2-(2-phenylprop-2-en-1-yl)-cyclohexan-1-ol (86): In a 50 mL dry roundbottomed flask, 2-(2-phenylprop-2-en-1-yl)-cyclohexan-1-one **83** (3.0 mmol, 0.64 g) was flushed with nitrogen, then distilled tetrahydrofuran (5 mL) was added via syringe. Vinyl magnesium bromide (6.0 mmol, 6 mL, 1.0 M in tetrahydrofuran) was added dropwise via syringe at room temperature and the solution was stirred overnight. The solution was quenched with 1M HCl and the aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with saturated aqueous sodium bicarbonate and brine, then dried with magnesium sulfate and concentrated under vacuum to a crude orange oil (0.72 g). After column chromatography (silica gel, 3:1 petroleum ether/diethyl ether), product **86** was isolated as a yellow oil in 11% yield (0.033 mmol, 0.081 g). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **86** was about 75% pure.

MS (EI, 70 eV, rel.%): 243 (13, M+1), 242 (12, M^{+}), 225 (94), 224 (100, loss of OH), 211 (31), 196 (44), 91 (4), 77 (3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.43-7.29 (m, 5H), 5.89 (dd, J=17.0, 11.0 Hz, 1H), 5.37 (dd, J=17.0, 1.5 Hz, 1H), 5.30 (dd, J=1.5, 0.5 Hz, 1H), 5.22 (dd, J=11.0, 1.5 Hz, 1H), 5.01 (dd, J=1.5, 1.5 Hz, 1 H), 2.95 (br d, J=14.0 Hz, 1H), 2.14 (dd, J=14.0, 11.0 Hz, 1H), 1.74-1.08 (m, 10 H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 147.1 (C), 145.8 (CH), 141.0 (C), 128.2

(CH, 2C), 127.2 (CH), 126.2 (CH, 2C), 114.1 (CH_2), 112.1 (CH_2), 74.6 (C), 41.6 (CH), 39.1 (CH_2), 35.9 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 21.3 (CH_2).



Reference: Halterman, R. L.; Ramsey, T. M. *J. Organomet. Chem.* **1994**, *465* (1-2), 175-179.

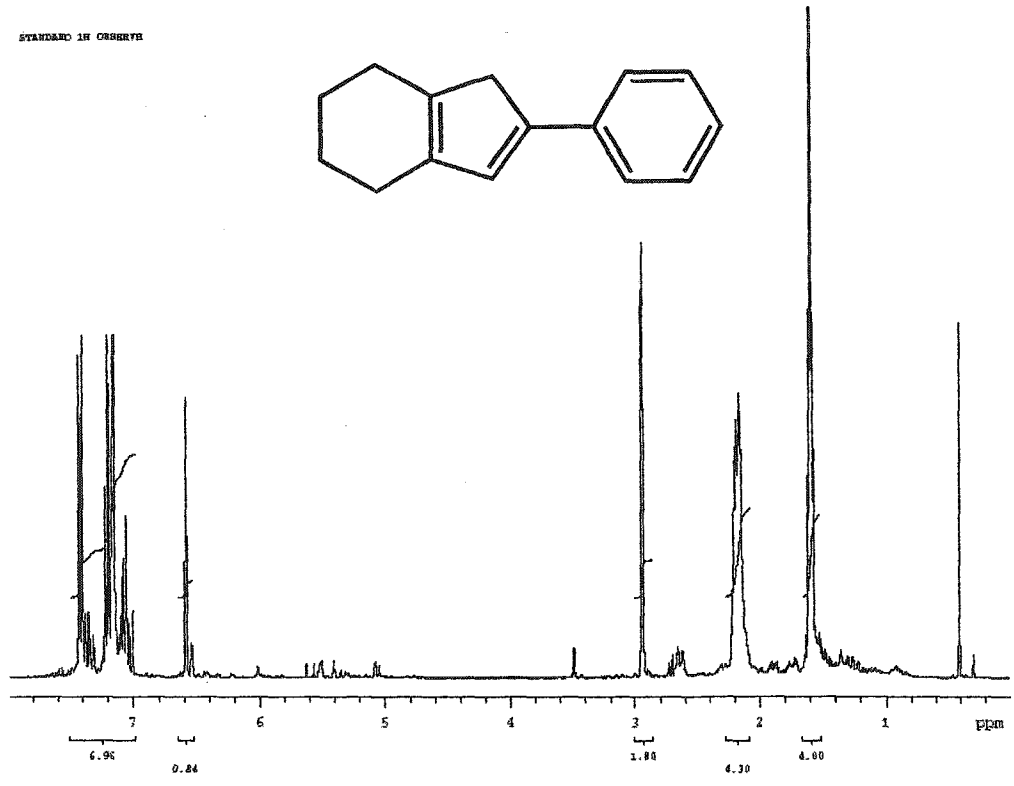
1H-2-Phenyl-4,5,6,7-tetrahydroindene (77): A dry 25 mL Schlenk flask was charged with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-ylidene][benzylidene]ruthenium(IV) dichloride, also known as Grubb's II Catalyst, **44** (0.000016 mol, 0.014 g) and 2 mL of distilled benzene-d_6 solvent under inert atmosphere. In a dry 25 mL flask, 1-ethenyl-2-(2-phenylprop-2-en-1-yl)-cyclohexan-1-ol **86** (0.00031 mol, 0.075 mg) was placed under argon. The purple benzene-d_6/catalyst solution was transferred via cannula to the 25 mL flask, then returned to the Schlenk flask after mixing with the 1-ethenyl-2-(2-phenylprop-2-en-1-yl)-cyclohexan-1-ol **86**. The mixture was stirred in a 65 °C oil bath for 18 h with a bubbler attached to release ethene gas. The solution was passed through silica gel with benzene-d_6 solvent and NMR spectral data was collected on the fractions. After NMR spectral characterization, the fractions containing product were combined and the solvent was removed under vacuum. Pure product **77** was isolated as colorless crystals (0.000051 mol, 0.010 g) in 17% yield. Pure starting material **86** was also recovered (0.00011 mol, 0.026 g). The yield after subtraction of this starting material is 26%. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **77** was greater than 90% pure.

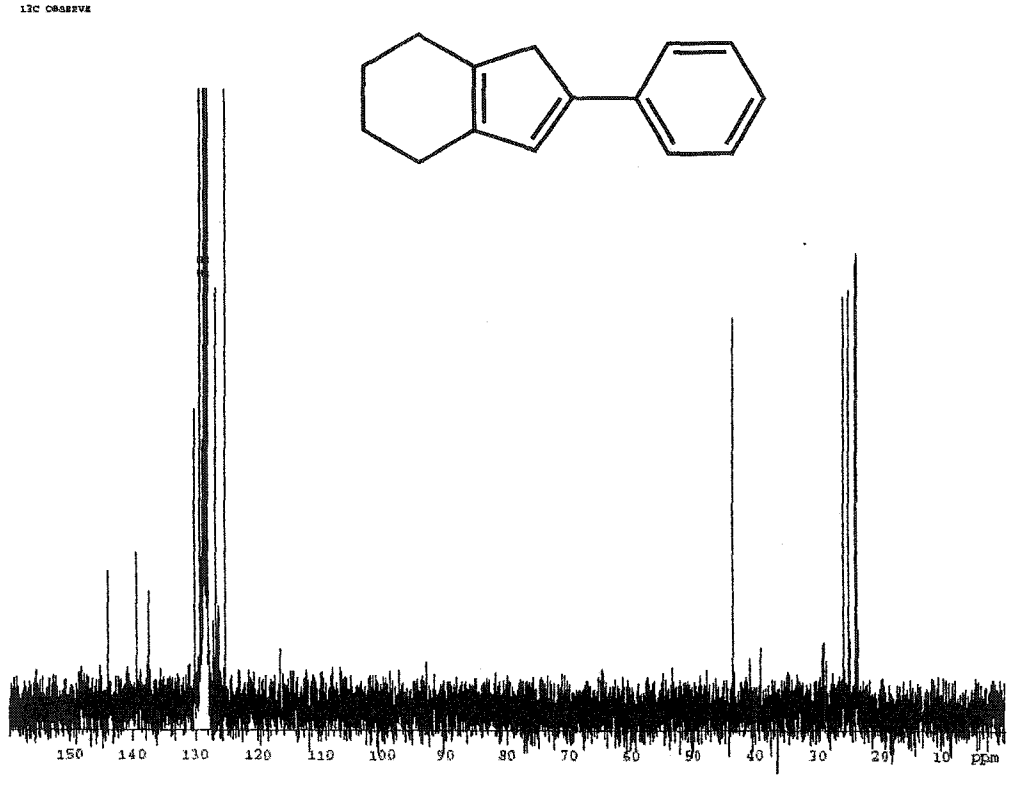
MS (EI, 70 eV, rel.%): 196 (100, M^+), 180 (59), 167 (28), 153 (9), 117 (6).

^{1}H-NMR (300 MHz, C_6D_6) δ: 7.41 (d, J=7.5 Hz, 2H), 7.19 (dd, J=7.5, 7.5 Hz, 2H),

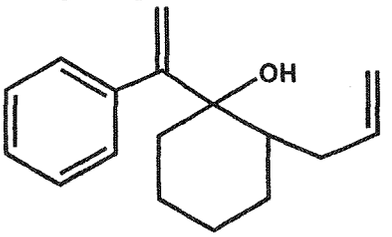
7.05 (dd, J=7.5, 7.5 Hz, 1H), 6.58 (s, 1H), 2.35 (br d, J=1.0 Hz, 2H), 2.17 (m, 4H), 1.58 (m, 4H).

^{13}C-NMR (300 MHz, C_6D_6, DEPT) δ: 143.9 (C), 139.3 (C), 137.5 (C), 130.1 (CH), 129.2 (CH, 2C), 129.0 (C), 126.7 (CH), 125.4 (CH, 2C), 43.6 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 24.0 (CH_2), 23.8 (CH_2).


STANDARD 1H OBSERVE
7
6
5
4
3
2
1
ppm
6.96
0.84
1.88
4.30
4.00


13C OBSERVE
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130
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110
100
90
80
70
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50
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ppm

Compound **89**: Listed following compound **90**



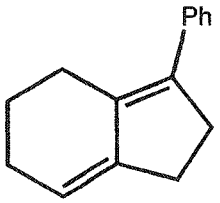
1-(1-Phenylethen-1-yl)-2-(prop-2-en-1-yl)-cyclohexan-1-ol (90):

In a dry 100 mL roundbottomed flask with a reflux condenser attached, crushed magnesium turnings (0.05 mol, 1.22 g) were flushed with nitrogen, then α-bromostyrene (0.05 mol, 9.1 g) and distilled tetrahydrofuran (50 ml) were added via syringe. The mixture was vigorously stirred and refluxed for 16 hours, then was cooled to room temperature. In a dry 250 mL flask, 2-(prop-2-en-1-yl)cyclohexanone **78** (0.02 mol, 2.76 g) was flushed with nitrogen and diluted in distilled tetrahydrofuran (20 mL) before the cooled Grignard reagent was added via cannula. After stirring at room temperature overnight, the solution was quenched with 1.0 M HCl and extracted with three portions of diethyl ether. The combined organic extracts were washed with water and brine, then dried with magnesium sulfate and the solvent was removed by vacuum. Column chromatography (silica gel, 2:1 petroleum ether/dichloromethane) resulted in a mixture of the ketone starting material and alcohol product. Under a strong vacuum the ketone starting material was removed, and product was isolated (0.0067, 1.61 g) in 33% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **90** was greater than 95% pure.

MS (TOF ES+, rel.%): 265 (89, $[M+Na]^+$), 242 (5, M^+), 225 (38, loss of OH), 183 (43), 111 (23), 105 (4).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.26-7.38 (m, 5H), 5.84 (dddd, J= 5.5, 8.5, 10.0, 17.0 Hz, 1H), 5.56 (d, J=1.5 Hz, 1H), 5.12 (d, J=1.5 Hz, 1H), 5.08 (m, 2H), 2.54 (dddt, J=1.0, 1.0, 4.0, 5.5, 14.0 Hz, 1H), 1.98 (ddd, J=9.0, 9.5, 14.0 Hz, 1H), 1.55-1.79 (m, 8H), 1.39 (ddt, J= 2.5, 12.0, 12.0, 12.5 Hz, 1H), 1.18 (m, 1H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 156.6 (C), 141.7 (C), 137.6 (CH), 128.7 (CH, 2C), 127.7 (CH, 2C), 126.9 (CH), 115.8 (CH_2), 114.2 (CH_2), 77.2 (C), 41.1 (CH), 38.9 (CH_2), 35.0 (CH_2), 26.7 (CH_2), 25.6 (CH_2), 21.5 (CH_2).

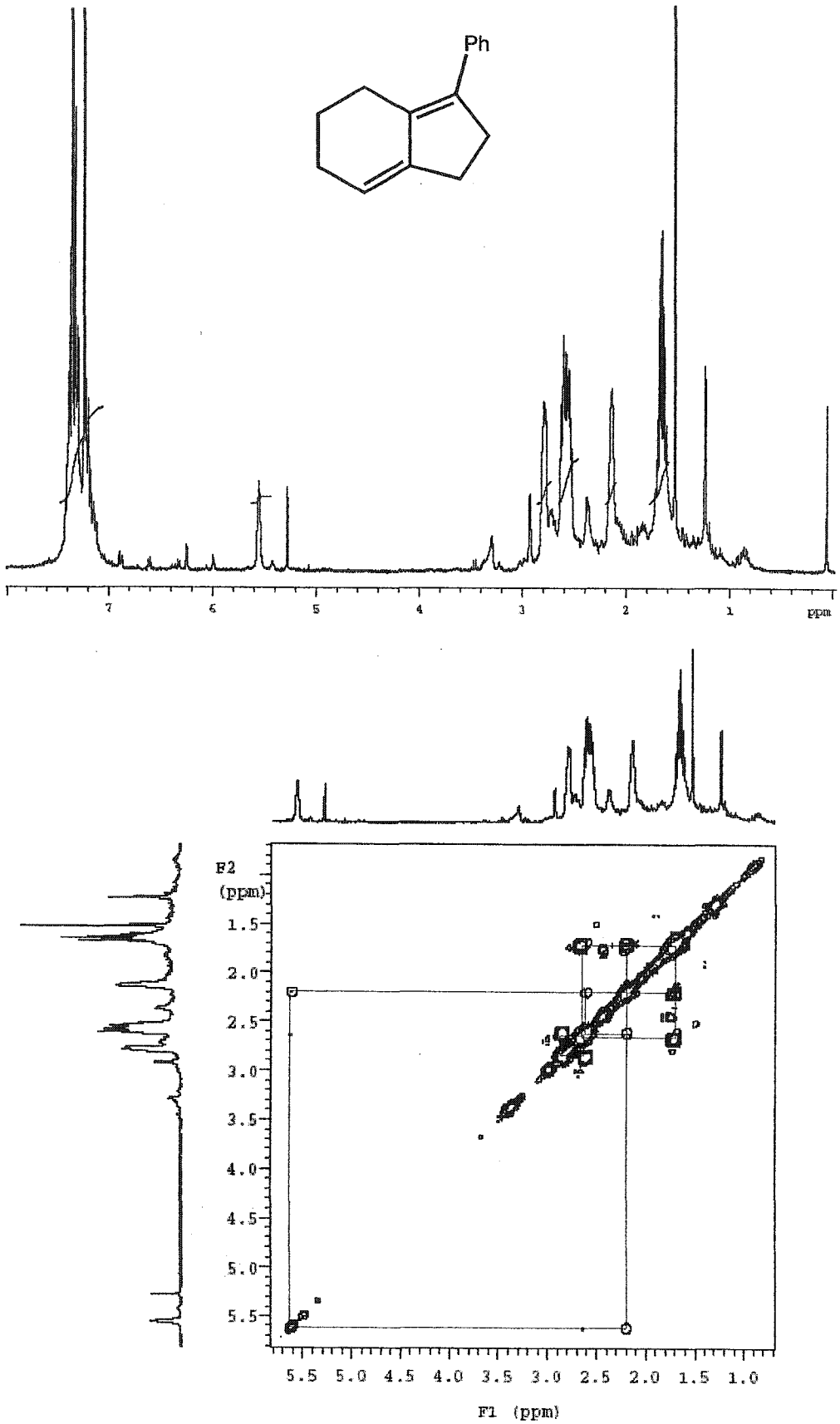


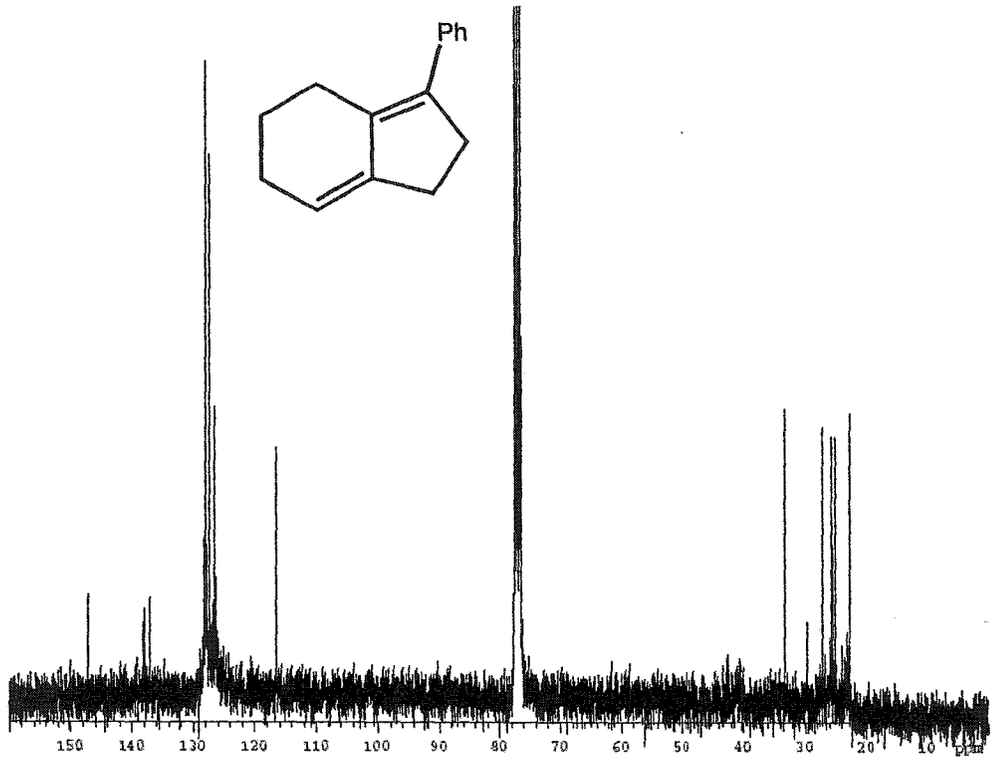
1-Phenylbicyclo[4.3.0]nona-1,5-diene (89): A dry 250 mL Schlenk flask was charged with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-ylidene][benzylidene]ruthenium(IV) dichloride, also known as Grubb's II Catalyst, **44** (0.000096 mol, 0.082 g) under inert atmosphere. In a dry 250 mL flask, 1-(1-phenylethen-1-yl)-2-(prop-2-en-1-yl)-cyclohexan-1-ol **90** (0.0014 mol, 330 mg) was placed under argon and diluted in 120 mL of distilled benzene. The solution was transferred via cannula to the 250 mL Schlenk flask. The mixture was stirred in a 75 °C oil bath for 60 h with a bubbler attached to release ethene gas, then the benzene was removed by vacuum. The crude mixture was passed through silica gel with dichloromethane. Product **89** was isolated as yellow oil (0.00028 mol, 0.055 g) in 20% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **89** was about 80% pure.

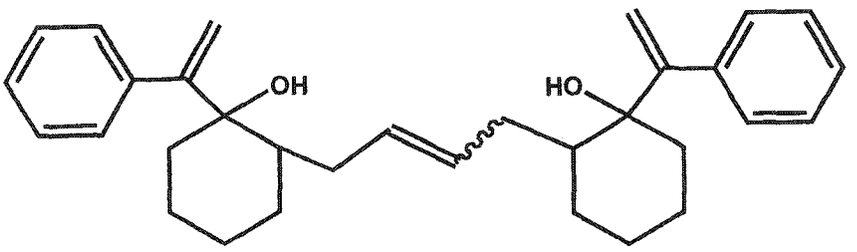
MS (EI, 70 eV, rel.%): 196 (M^{+}, 100), 167 (84), 153 (29), 91 (4).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.41-7.15 (m, 5H), 5.56 (m, 1H), 2.80 (m, 2H), 2.64-2.52 (m, 4H), 2.14 (m, 2H), 1.70-1.61 (m, 2H).

^{13}C-NMR (300 MHz, $CDCl_3$) δ: 147.2, 137.9, 128.1 (3C), 127.4 (2C), 126.5, 116.6, 33.2, 27.2, 25.6, 25.1, 22.8.


Ph
7
6
5
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2
1
ppm
F2
(ppm)
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2.0
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3.0
3.5
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4.5
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5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F1 (ppm)


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10

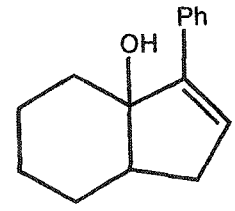


(*E*)- and (*Z*)-1,4-Bis[1-(1-phenylethen-1-yl)cyclohexan-1-ol-2-yl]but-2-ene (91): A dry 25 mL Schlenk flask was charged with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-ylidene][benzylidene]ruthenium(IV) dichloride, also known as Grubb's II Catalyst, **44** (0.000031 mol, 0.026 g) and 2 mL of distilled benzene-d_6 solvent under inert atmosphere. In a dry 25 mL flask, 1-(1-phenylethen-1-yl)-2-(prop-2-en-1-yl)-cyclohexan-1-ol **90** (0.00062 mol, 0.150 mg) was placed under argon. The purple benzene-d_6 /catalyst solution was transferred via cannula to the 25 mL flask then returned to the Schlenk flask after mixing with the 1-(1-phenylethen-1-yl)-2-(prop-2-en-1-yl)-cyclohexan-1-ol **90**. The mixture was stirred in a 55 °C oil bath for 18 h with a bubbler attached to release ethene gas. The solution was passed through silica gel with benzene-d_6 solvent and NMR spectral data was collected on the fractions. After NMR spectral characterization, the fractions containing product were combined and the solvent was removed under vacuum. Product **91** was isolated as a brown oil (0.000035 mol, 0.016 g) in 11% yield. Pure starting material **90** was also recovered (0.00012 mol, 0.029 g). The yield after subtraction of this starting material is 14%. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **91** was about 80% pure.

MS (TOF ES+, rel.%): 479 (100, $[M+Na]^+$), 439 (3, loss of OH), 421 (3, loss of OH), 237 (22), 197 (17), 98 (22).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29-7.25 (m, 6H), 7.21-7.16 (m, 4H), 5.46 (dd, J=0.5, 2.0 Hz, 2H), 5.35 (m, 2H), 5.02 (d, J=2.0 Hz, 2H), 2.37 (d, J=13.5 Hz, 2H), 1.84 (m, 2H), 1.70-1.46 (m, 16H), 1.29 (m, 2H), 1.11 (m, 2H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 156.7 (C, 4C), 141.7 (C, 4C), 130.42 (CH, 2C), 130.38 (CH, 2C), 128.8 (CH, 8C), 127.7 (CH, 8C), 126.9 (CH, 4C), 114.1 (CH_2, 4C), 77.34 (C, 2C), 77.31 (C, 2C), 41.58 (CH, 2C), 41.55 (CH, 2C) 38.92 (CH_2, 2C), 38.87(CH_2, 2C), 33.79 (CH_2, 2C), 33.75 (CH_2, 2C), 26.85 (CH_2, 2C), 26.82 (CH_2, 2C), 25.7 (CH_2, 4C), 21.6 (CH_2, 4C).

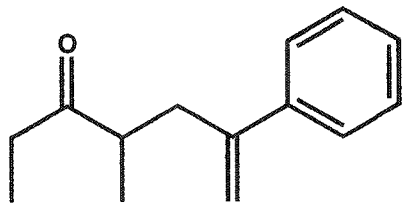


1-Phenylbicyclo[4.3.0]-non-7-en-9-ol (92): A dry 250 mL Schlenk flask was charged with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-ylidene][benzylidene]ruthenium(IV) dichloride, also known as Grubb's II Catalyst, **44** (0.00016 mol, 0.14 g) under inert atmosphere. In a dry 250 mL flask, 1-(1-phenylethen-1-yl)-2-(prop-2-en-1-yl)-cyclohexan-1-ol **90** (0.0020 mol, 500 mg) was placed under argon and diluted in 200 mL of distilled benzene. The solution was transferred via cannula to the 250 mL flask. The mixture was stirred in a 70 °C oil bath for 18 h with a bubbler attached to release ethene gas, then the benzene was removed by vacuum. The crude mixture was passed through silica gel with dichloromethane. Product was isolated as yellow oil (0.0004 mol, 0.085 g) in 20% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **92** was about 75% pure.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.44 (d, J=6.5 Hz, 2H), 7.33-7.30 (m, 3H), 6.06 (dd, J=2.0, 2.5 Hz, 1H), 2.25 (m, 2H), 1.90-1.60 (m, 6H), 1.42-1.22 (m, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 136.1 (C), 131.7 (CH), 128.2 (CH, 2C), 127.0 (CH), 126.7 (CH, 2C), 81.9 (C), 50.2 (CH), 34.0 (CH_2), 33.7 (CH_2), 25.9 (CH_2), 24.5 (CH_2), 21.3 (CH_2).

Treatment of this product **92** in $CDCl_3$ with *para*-toluenesulfonic acid at room temperature resulted in immediate conversion to 1-phenylbicyclo[4.3.0]nona-1,5-diene **89**.



4-Methyl-6-phenylhept-6-en-3-one (93):

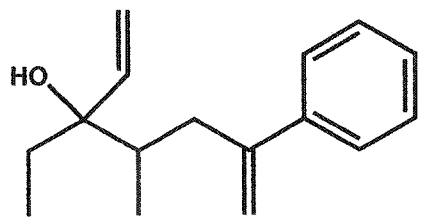
In a dry 50 mL roundbottomed flask, diisopropylamine (0.0060 mol, 0.61 g) was flushed with nitrogen and distilled tetrahydrofuran (10 mL) was added via syringe. After the solution was cooled to -78 °C with a dry ice/acetone bath, *n*-butyllithium (0.0058 mol, 2.4 mL, 2.46 M in hexane) was added dropwise via syringe. The solution was allowed to warm to room temperature over 15 min, and was returned to -78 °C before 3-pentanone (0.0048 mol, 0.47g) in distilled tetrahydrofuran (5 mL) was added dropwise via syringe. The pale yellow solution was stirred for two hours at -78 °C, then was warmed to room temperature and 1-bromo-2-phenylprop-2-ene **82** (0.0050 mol, 0.99g) in distilled tetrahydrofuran (3 mL) was added rapidly via syringe. The red solution was left stirring at room temperature overnight. The solution was quenched with water and extracted with three portions of diethyl ether. The combined organic extracts were washed with water and brine, then dried with magnesium sulfate. After removal of the solvent by vacuum, a crude orange oil was isolated (0.84 g). After column chromatography (silica gel, 1:2 petroleum ether/dichloromethane, then pure dichloromethane), pure product was isolated as a yellow oil in 27% yield (0.0013 mmol, 0.260 g). Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **93** was greater than 95% pure.

MS (EI, 70 eV, rel.%): 203 (100, $[M+H]^+$), 185 (59, loss of OH), 145 (94), 117

(6), 91 (3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31-7.15 (m, 5H), 5.19 (d, J=1.5 Hz, 1H), 4.97 (dt, J=1.0, 1.5, 1.5 Hz, 1H), 2.86 (ddd, J=1.5, 6.5, 14.0 Hz, 1H), 2.54 (ddq, J=6.5, 6.5, 7.0 Hz, 1H), 2.34 (ddd, J=1.0, 6.5, 14.0 Hz, 1H), 2.26 (q, J=7.5 Hz, 1H), 0.96 (d, J=7.0 Hz, 3H), 0.90 (t, J=7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 214.5 (C), 146.0 (C), 140.4 (C), 128.3 (CH, 2C), 127.5 (CH), 126.1 (CH, 2C), 114.5 (CH_2), 44.0 (CH), 38.7 (CH_2), 34.7 (CH_2), 16.7 (CH_3), 7.5 (CH_3).



3-Ethyl-4-methyl-6-phenylhept-1,6-dien-3-ol (94):

In a 50 mL dry roundbottomed flask, 4-methyl-6-phenylhept-6-en-3-one **93** (2.4 mmol, 0.49 g) was flushed with nitrogen, then distilled tetrahydrofuran (5 mL) was added via syringe. Vinyl magnesium bromide (3.6 mmol, 3.6 mL, 1.0 M in tetrahydrofuran) was added dropwise via syringe at room temperature and the solution was stirred overnight. The solution was quenched with 1M HCl and the aqueous phase was extracted with three portions of diethyl ether. The combined organic portions were washed with water and brine, then dried with magnesium sulfate and concentrated under vacuum to a crude yellow oil (0.46 g). A 0.30 g portion of this crude oil was purified by column chromatography (silica gel, 3:1 petroleum ether/diethyl ether). Product was isolated as a yellow oil (0.00047 mmol, 0.109 g) along with a pure side product, 4-methyl-6-phenylhept-6-en-3-ol, which had resulted from reduction of the ketone starting material (0.00049 mol, 0.100 g). The yields for product and side product were 30% and 31%, respectively. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compound **94** was about 90% pure.

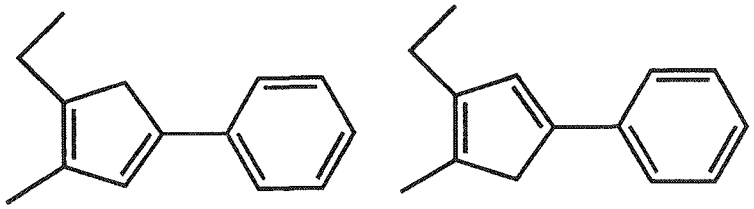
MS (EI, 70 eV, rel.%): 230 (M^{+}, 2), 229 (8), 211 (22), 198 (88), 131 (100).

Mixture of diastereomers (1:1.3 ratio):

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24-7.46 (m, 10H), 5.83 (dd, J=11.0, 17.0 Hz,

1H), 5.82 (dd, J=11.0, 17.0 Hz, 1H), 5.31 (m, 6H), 5.07 (m, 2H), 3.11 (br d, J=14.5 Hz, 1H), 2.99 (br d, J=14.0 Hz, 1H), 2.05 (ddd, J=4.5, 11.5, 14.0 Hz, 2H), 1.60 (m, 6H), 1.50 (s,1H), 1.39 (s, 1H), 0.85 (t, J=7.5Hz, 3H), 0.84 (t, J=7.5 Hz, 3H), 0.82 (d, J=7.0 Hz, 6H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 147.75 (C), 147.65 (C), 142.4 (CH), 141.3 (CH), 141.0 (C), 140.8 (C), 128.2 (CH, 4C), 127.3 (CH, 2C), 126.3 (CH, 4C), 114.1 (CH_2), 114.0 (CH_2), 113.51 (CH_2), 113.48 (CH_2), 77.9 (C, 2C), 39.3 (CH), 38.9 (CH), 37.4 (CH_2), 36.8 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 14.0 (CH_3), 12.5 (CH_3), 7.6 (CH_3), 7.3 (CH_3).



1-Ethyl-2-methyl-4-phenylcyclopenta-1,3-diene (96b) and 2-Ethyl-1-methyl-4-phenylcyclopenta-1,3-diene (96a):

A dry 25 mL Schlenk flask was charged with tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-ylidene][benzylidene]ruthenium(IV) dichloride, also known as Grubb's II Catalyst, **44** (0.000022 mol, 0.018 g) under inert atmosphere. In a dry 25 mL flask, 3-ethyl-4-methyl-6-phenylhept-1,6-dien-3-ol **94** (0.000434 mol, 0.100 mg) was placed under argon, then 2 mL of distilled benzene was used to transfer this starting material into the Schlenk flask. A bubbler was attached and upon heating the solution in a 70 °C oil bath, immediate foaming occurred and the vigorous bubbling of ethene from the solution lasted for 15 minutes. The solution was left stirring at 70 °C for 48 h under argon, then the benzene was removed by vacuum. The crude mixture was passed through silica gel with dichloromethane. A mixture of cyclopentadiene isomers (1.7:1.0 ratio) was isolated as a yellow oil (0.00015 mol, 0.028 g) in 35% yield. Inspection of the ^{1}H-NMR and ^{13}C-NMR spectra indicated compounds **96a/96b** were about 85% pure.

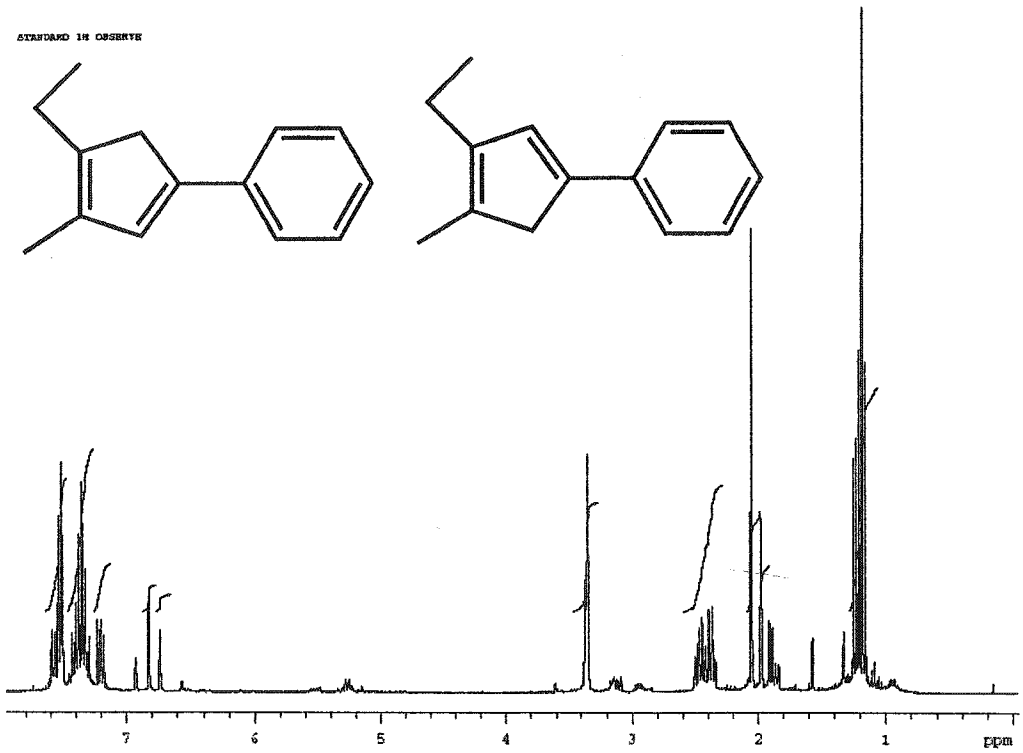
MS (EI-DIP, 70 eV, rel.%): 184 (M^{+}, 100), 169 (81), 155 (39), 105 (92), 91 (48), 77 (52).

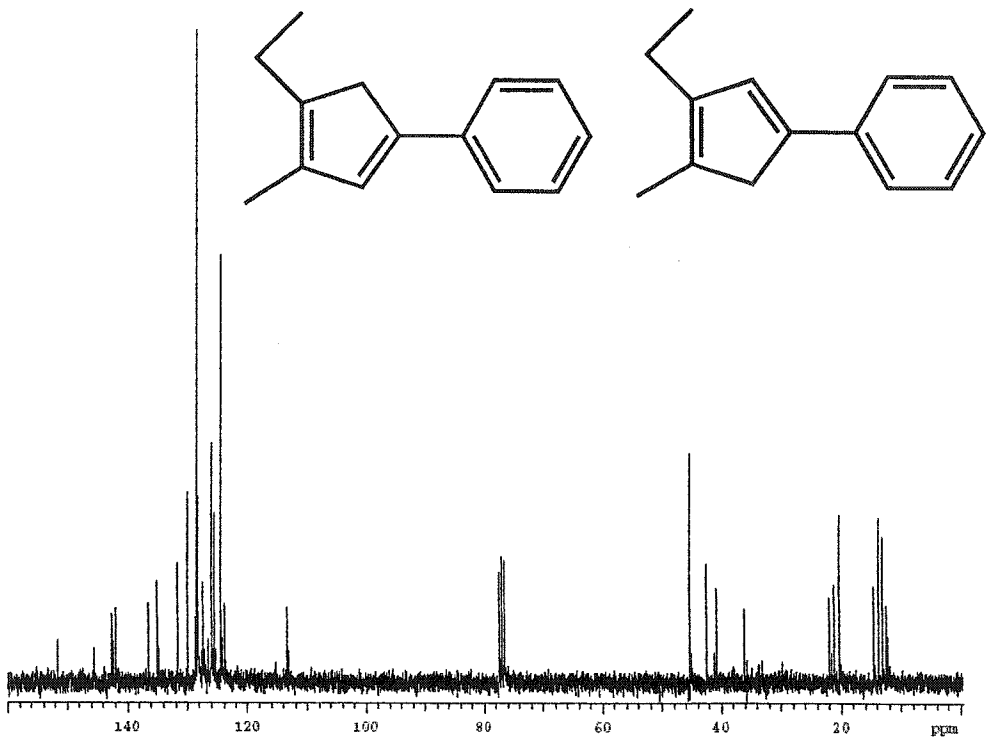
Mixture of isomers (1.7:1 ratio):

Major isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, J=7.0 Hz, 2H), 7.40 (m, 2H), 7.20 (t, J=7.0 Hz, 1H), 6.74 (s, 1H), 3.37 (m, 2H), 2.46 (q, J=7.5 Hz, 2H), 2.05 (s, 3H), 1.23 (t, J=7.5 Hz, 3H).

Minor isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, J=8.0 Hz, 2H), 7.35 (dd, J=7.0 Hz, 8.0 Hz, 2H), 7.20 (dd, J=7.0, 8.0 Hz, 1H), 6.83 (s, 1H), 3.35 (br d, J=0.5 Hz, 2H), 2.38 (q, J=7.5 Hz, 2H), 1.98 (br s, 3H), 1.18 (t, J=7.5 Hz, 3H).

^{13}C-NMR (300 MHz, $CDCl_3$, DEPT) δ: 142.6 (C), 141.9 (C), 136.4 (C), 135.0 (C), 131.7 (CH), 130.0 (CH), 128.5 (CH, 4C), 128.5 (C, 2C), 128.4 (C), 127.5 (C), 125.9 (CH, 2C), 124.5 (CH, 4C), 45.3 (CH_2), 42.5 (CH_2), 22.0 (CH_3), 21.2 (CH_2), 20.3 (CH_2), 13.9 (CH_3), 13.3 (CH_3), 12.5 (CH_3).


STANDARD 1H OBSERVE
7
6
5
4
3
2
1
ppm


140
120
100
80
60
40
20
ppm

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