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SYNTHETIC AND MECHANISTIC ASPECTS OF ZIEGLER-NATTA POLYMERIZATION: REGIO- AND DIASTEREOSELECTIVE FORMATION OF FIVE- AND SIX-MEMBERED CARBOCYCLES

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SYNTHETIC AND MECHANISTIC ASPECTS OF ZIEGLER-NATTA POLYMERIZATION: REGIO- AND DIASTEREOSELECTIVE FORMATION OF FIVE- AND SIX-MEMBERED CARBOCYCLES

By

Jonathan Russell Young

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ABSTRACT

SYNTHETIC AND MECHANISTIC ASPECTS OF ZIEGLER-NATTA POLYMERIZATION: REGIO- AND DIASTEREOSELECTIVE FORMATION OF FIVE- AND SIX-MEMBERED CARBOCYCLES

By

Jonathan Russell Young

An ongoing project in our group involves the development and application of novel ring-forming reactions that feature intramolecular addition of reactive carbon intermediates to unactivated olefins. Although ring-forming methods utilizing this synthetic design are known, none of these methods were able to combine high regio- and stereoselective qualities that spanned applicability to synthesis of both five- and six-membered rings. Our objective was to develop a general, complimentary ring-forming method that exhibited high selectivities for a variety of ring sizes. We focused our attention on the use of organometallic intermediates as a means of directing both the regio- and stereochemistry. The organometallic complexes chosen were those of alkyltitanocene chlorides, which are well known for undergoing efficient and stereoselective α-olefin polymerization.

Our initial goal was to ascertain the regioselectivity of olefin insertion into the carbon-titanium bond for the unsubstituted 5-hexen-1-yl- and 6-hepten-1-yltitanocene chlorides. These alkyltitanocene derivatives were stable for weeks

and exhibited no tendency toward olefin insertion. However, activation with $EtAlCl_2$ drastically altered the electronic environment surrounding the metal and the reactivity of these complexes towards olefin insertion. As a consequence of the Lewis acid additive, facile olefin insertion resulted with exclusive *exo* specificity in each case, providing methylcyclopentane (5-*exo*-trig, 95% yield) and methylcyclohexane (6-*exo*-trig, 75% yield) after hydrolysis.

We next turned our attention to the stereochemical consequence of the carbon-carbon bond formation with respect to an alkyl substituent on the tether. In the case of cyclopentane formation, selectivity ranged from 97:3 to >99:1 for 2-, 3-, and 4-methyl-5-hexen-1-yltitanocene chlorides. The stereocontrol exhibited for the six-*exo*-trig cyclizations were more complex, due to the greater flexibility of the alkyl tether. Cyclization of 4- and 5-methyl-6-hepten-1-yltitanocene chlorides resulted in >98:2 diastereomeric ratio of dimethylcyclohexanes. However, when a methyl group was β or γ to the metal, cyclization was less successful (82:18, and 50:50 trans:cis, respectively). Yet with an isopropyl group in these positions, enhanced olefin facial selectivity was observed (92:8, trans:cis and 74:26, cis:trans, respectively).

In the course of developing this synthetic methodology, we noticed that olefin insertion was more facile for a certain substitution pattern. The substrates that appeared to be more reactive had a common structural feature, an alkyl substituent on the carbon β to titanium. We have developed a series of competitive rate experiments to determine if α- or β-hydrogen activation plays a role in the cyclization process. At this stage of the project, optimization of the experimental conditions is in progress.

To Mom, Dad, Nancy, and Karl

Mom and Dad, thank you for always being there when I needed you. You two have been terrific parents and have always been my biggest supporters. From every hockey, baseball, or football games, to drama and band concerts, you were always there. I can never adequately express what your love and support has meant to me.

Nancy, thank you for your patience and allowing me to fulfill my dreams during the past years. I know these years have been difficult for us, but let's be happy we survived them, together. I am sorry that we didn't always have as much time with each other as we wanted, but remember, brighter days and opportunities await us in Madison. Let's have some fun as a family.

Karl, thank you for all the happiness you constantly bring into our lives. I want you to never be afraid to chase your dreams.

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I would first of all like to thank the anonymous person in the Natural Resources office that studied my application so thoroughly during the months of February to late October of 1987. I made it here anyway!

I will be forever indebted to Dr. Stille (that is John, now) for all that he taught me. I will always miss our long conversations in the morning over a cup of coffee, weightlifting and running at the crack of dawn, and the enthusiasm that we shared together in pursuit of common goals. Chemistry aside, your friendship is something very special to me. Thanks for all that you have done and given to me. Please stay in touch in the years to come.

I want to wish the best to all of my friends in the Stille group. Greg and Art, good luck at Stanford and say hi to Barry for me. Polymervanan, thanks for the midnight brainstorming, it was a lot of fun.

Words cannot express the wonderful friend and person I met at MSU. Nancy, you provided a wonderful spark to not only me, but to the whole group. All the help and support you gave me over the last two years meant so much to me. I clearly could not have survived this dissertation without your proofreading skills or your daily positive attitude and kind words of encouragement. Thank you for all you have done and most of all, for believing in me. My morning donut will certainly not be the same anymore but it will remind be of countless special mornings we shared. How will I cool my coffee without you? You are the best friend I could ever have asked for and I will miss you very much.

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LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
Bu	Butyl
n-BuLi	n-Butyllithium
t-BuLi	*tert*-Butyllithium
C_6H_6	Benzene
Cp	Cyclopentadienyl
mCPBA	meta-Chloroperbenzoic acid
D	Deuteron (^2H)
DiBAl	Diisobutylaluminum hydride
DCE	1,2-Dichloroethane
DIPA	Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Methyl sulfoxide
Et	Ethyl
Et_2O	Diethyl ether
LAD	Lithium aluminum deuteride
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
MAO	Methaluminoxane $(O\text{-}Al(Me))_n$
Me	Methyl

Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
$Ni[COD]_2$	Nickel cyclooctadiene
Ph	Phenyl
PMDTA	N, N, N', N", N"-Pentamethyldiethylenetriamine
Pr	Propyl
iPr	Isopropyl
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethylenediamine
SET	Single Electron Transfer

INTRODUCTION

1. Outline of the Synthetic Problem

Carbocycles of the quinane and steroid families have presented chemists with a number of interesting synthetic challenges. The efforts exerted toward the preparation of these medicinally useful compounds have benefited chemists and non-chemists alike. Upon examination of the complex architectural framework of the quinanes and steroids, a common theme woven throughout these families of compounds was the repetition of five- and six-membered ring subunits, fused together in a variety of regio- and stereochemical patterns. To effectively launch an assault on quinane or steroid targets, a strategic plan must be devised for the efficient construction of the carbocyclic skeleton. This plan should address, not only the preparation of five- and six-membered rings but to also incorporate the numerous stereocenters as well. An inspired plan would be one that could achieve both of these goals simultaneously, thus minimizing the number of manipulations. Although many valuable ring-forming methods exist for achieving any one of these goals, a single, general method applicable to five- and six-membered rings with good control over regio- and stereochemistry would be useful. Our interest in preparing compounds of the above variety has compelled us to develop a general, yet selective, ring-forming method capable of fulfilling the aforementioned criteria. Our efforts have concentrated on

developing organotransition metal reagents to direct selective, intramolecular carbon-carbon bond construction.[1]

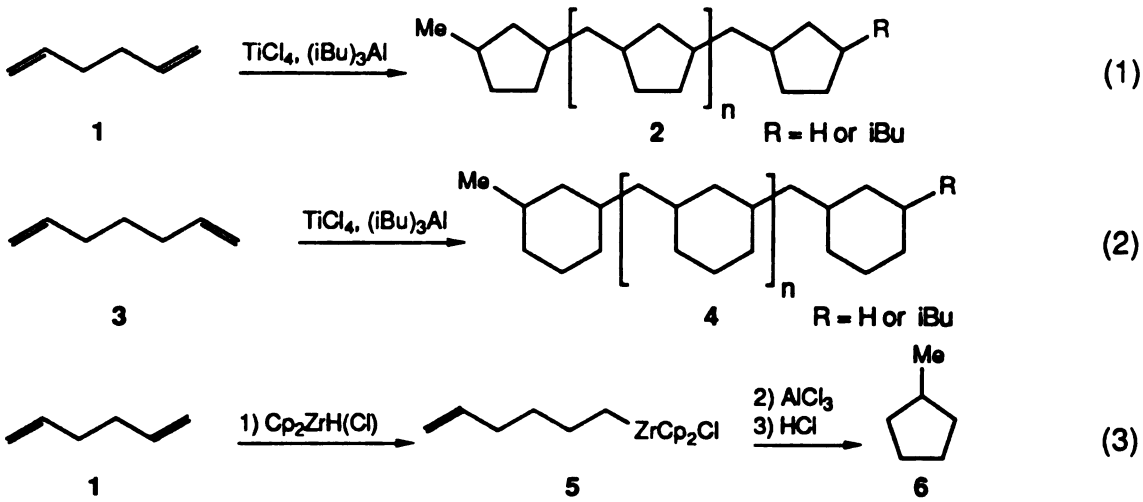
The interest in organometallic methods has been building ever since Grignard discovered the landmark reaction between alkyl halides and magnesium. The crucial observation was the novel change in the polarity of carbon (umpolung), and the useful reversal in the chemical reactivity of carbon. Grignard's efforts blossomed into an exciting new approach to carbon-carbon bond formation. Early in the development of organometallic chemistry, chemists were laying the groundwork, reacting various metals together with different organic substrates in an apparent random fashion. What resulted from this "hit or miss" approach was a firm foundation for understanding the interaction and subsequent reaction of organic functional groups with metal complexes.[2] As a result, very predictable methods for engineering carbon-carbon bond construction utilizing organometallic reagents have evolved. The sophistication of of organometallic reagents for carbon-carbon bond formation lies in the ability to fine tune the reactivity, and thus selectivity, of the metal complex by varying the steric and electronic environment surrounding the metal. This can be accomplished by judicious choice of the metal, its oxidation state, and the surrounding ligands.

One of the most useful and exploited organometallic processes is the reaction of alkyl-metal complexes with olefins. Certain electron deficient metal complexes, which have a vacant coordination site available, can form a π-complex with olefins and can often be induced to insert the olefin into the metal-carbon bond. In many cases, the carbon-carbon bond could be formed in a highly regio- and stereoselective manner. A good example is that of Ziegler-Natta polymerization.[3]

In the early 1950's, Ziegler[4] and Natta[5] independently discovered that titanium salts, in combination with alkyl aluminums, facilitated the polymerization of ethylene. The active polymerization catalyst was suggested to be an alkyltitanium species, formed by alkyl ligand exchange from aluminum to titanium. This proposal was later substantiated after the combined action of ethyltitanocene chloride[6] and ethylaluminum dichloride was shown to polymerize ethylene.[7]

Several reports have indicated that Ziegler-Natta chemistry should be well suited to ring forming reactions. In 1958, Marvel reported that 1,5-hexadiene was polymerized with $TiCl_4$ and an alkyl aluminum co-catalyst (eqn. 1).[8a] The polymer contained repeating units of methylenecyclopentanes, connected in a 1,3 relationship. Similarly, 1,6-heptadiene resulted in a polymer of methylenecyclohexanes under the same conditions (eqn. 2). Thus, each intermolecular olefin insertion was followed by an intramolecular insertion resulting in carbocycle formation. At this point, the stereochemical details of this reaction have not been determined. More recently, Waymouth has shown that a zirconocene catalyst, together with methaluminoxane (MAO), polymerized 1,5-hexadiene in the same fashion as in eqn. 1, yet polymerization of 1,6-heptadiene yielded only low molecular weight oligomers.[8b] There have been a number of paramount reports in which monomer formation was realized as well. It has been demonstrated that 5-hexen-1-ylmetal complexes (Metal = Ti, Zr, Sc, Y)[9] could be induced to isomerize to methylcyclopentylmetal products. Specifically, Grubbs described that $EtAlCl_2$ successfully catalyzed the intramolecular olefin insertion of 5-hexen-1-yltitanocene chloride to provide, after hydrolysis, high yields of methylcyclopentane (Scheme 13).[9a] In a similar fashion, Schwartz observed that when transmetallation of **5** to aluminum was attempted, methylcyclopentane was produced (eqn. 3).[9b] These results provide

convincing evidence to the viability of cyclopentane and cyclohexane formation *via* organometallic intermediates, yet leave many questions unanswered concerning the stereochemical details of the newly formed asymmetric center.



2. Background on the Synthetic Aspects of Current Cyclization Methodology

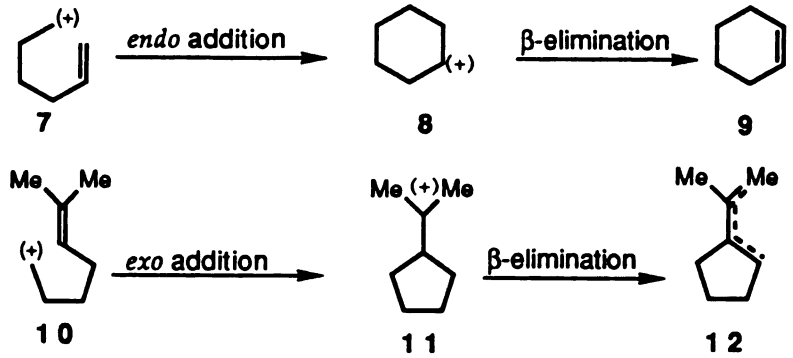
A number of ring-forming methods have been creatively designed in which a reactive carbon intermediate added across an unactivated olefin. The preparative utility of intramolecular addition of carbon centered radicals, anions, and cations, as well as covalently bound transition metals, to distal double bonds has been demonstrated. However, each of these methods had certain inherent limitations that diminished their applicability to general situations. An overview of various ring forming methods will be provided, addressing such issues as regioselectivity, stereoselectivity, generality to different ring sizes, and the ability to functionalize the final product. This discussion will begin by examining both carbocationic and anionic, as well as free radical approaches to carbocyclization. Lastly, organometallic carbocyclizations, in which the metal

was covalently bound to carbon, will be described for metals such as magnesium, aluminum, and palladium.

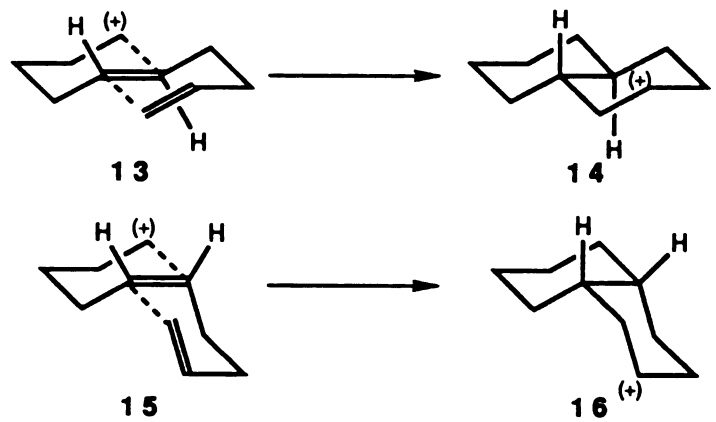
A. Carbocationic Cyclizations

The field of carbocationic cyclization was very active during 1960-75 because of its resemblance to nature's way of producing complex ring systems, such as steroids.[10] Both the regio- and stereochemistry were well defined and predictable. Generally, cyclization proceeded in an *endo* manner to form the larger ring, and a more stable carbocation (Scheme 1).[10] For example, cyclization of **7** formed a cyclohexene (**9**) rather than methylcyclopentane. However, five-membered rings have been formed when the substrate contained an appropriately placed substituent that could direct *exo* cyclization by producing a more stable carbocation. Thus, cyclization of **10** produced the product of *exo* addition (**11**), possibly due to the steric restriction of the *endo* pathway. The stereochemistry was found to be dependent on the stereochemistry of the olefins (Scheme 2).[10] Thus, a polyolefinated substrate that possessed trans olefins situated in a 1,5 relationship (see **13**) were found to undergo cyclization to produce trans fused six-membered rings (**14**). Similarily, cyclization of substrates with the corresponding cis arrangement (see **15**), resulted cis ring junctions (**16**).

Scheme 1. Regioselectivity of Carbocationic Cyclizations

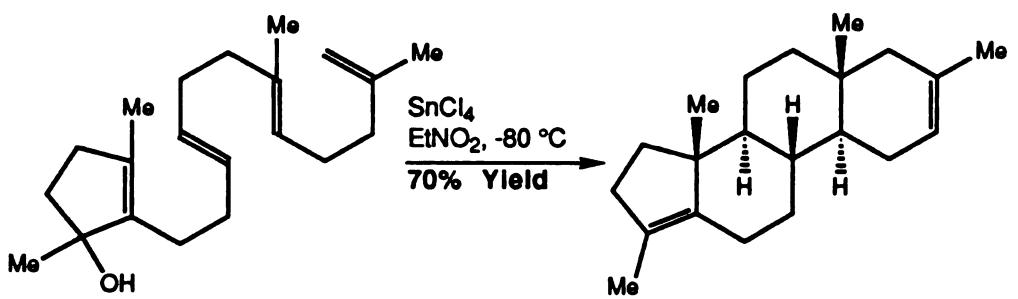


Scheme 2. Stereoselectivity of Carbocationic Cyclizations



Two other important design elements were crucial to cationic cyclization. Specifically, these two elements were a carbocation initiator and terminator. Treatment of a polyolefinated compound with a protic acid was found to be a poor method for selective carbocation formation due to the propensity of the acid to protonate indiscriminately, and to isomerize olefins.[10] However, the advent of Lewis acids in combination with either an acetal, epoxide, or an allylic alcohol, led to clean formation of the desired carbocation. The main function of the terminator was to direct the size of the final ring formed. Common terminators that have been used were alkyl, allyl, benzyl, or β-silyl groups. Alkyl groups proved useful for directing the size of the final ring, however, unselective β-elimination resulted in a number of alkene isomers (see **12**, Scheme 1). Allyl

and benzyl terminators alleviated this problem, but difficulty encountered in attempting to remove these unnatural steroid entities overshadowed this small success. Silyl groups were able to overcome both of these difficulties, owing to their well-known propensity to stabilize β-carbocations and to undergo β-silyl elimination. Thus, the strategic location of the silyl group served to selectively direct ring closure to form a β-carbocation, followed by rapid β-silyl elimination providing a single structural isomer.

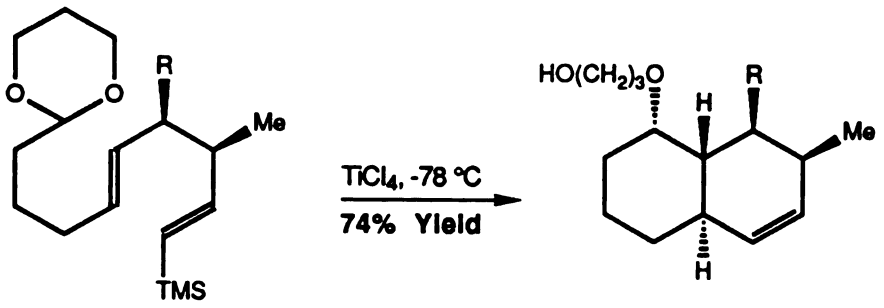


17 18 (4)

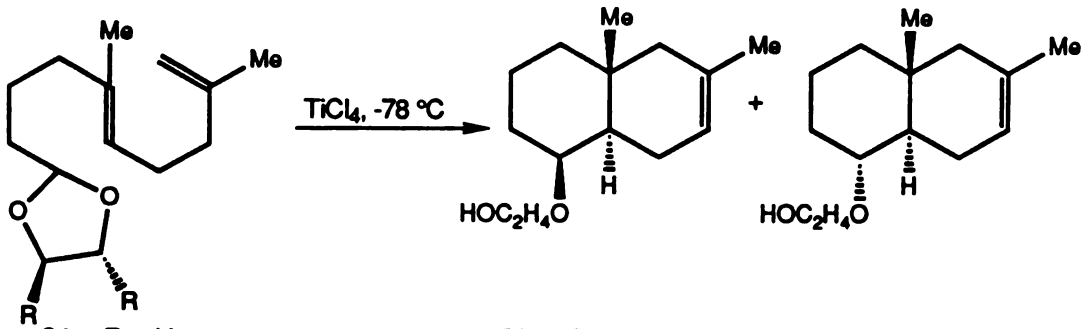
Johnson and co-workers were the first to apply the above principles for the complete formation of the steroid skeleton in a single tandem cyclization (eqn. 4).[10] Thus, treatment of allylic alcohol **17** with tin chloride resulted in the formation of three new rings in better than 70% yield (**18**). More importantly, five new chiral centers were produced that possessed the correct relative configuration of 16,17-dehydroprogesterone. More recently, Burke has used this methodology, equipped with a dioxane initiator and a vinyl silane terminator, as the key step in the synthesis of the decalin ring systems for mevinic acid (eqn. 5),[11a] nagilactones,[11b] (+)-dihydrocompactin and (+)-compactin,[11c] (+)-fragolide,[11d] and (-)-perinporin B.[11d]

Another attractive feature of carbocationic cyclization was the ability to affect enantioselective bond formation.[12] The simplicity with which chirality was introduced into the cyclization precursor was a major advantage. Thus, an

achiral alkenal was made chiral by trivial transformation to an acetal using a chiral diol (**21b**, eqn. 6). Cyclization of **21b** resulted in the normal ratio of diastereomeric isomers (see cyclization of **21a**) but with an excellent enantiomeric excess. The opposite absolute configuration was also available by using the other enantiomer of the diol.



19 **20** (5)



21a; R = H
21b; R = CH_3

22a; 90 (1:1)
22b; 90 (93:7)

23a; 10 (1:1)
23b; 10 (94:6)

(6)

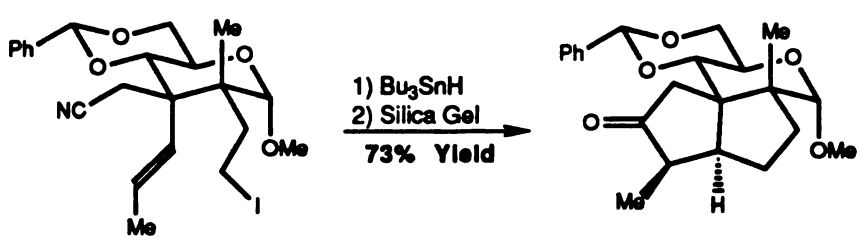
B. Free Radical Cyclizations

Free radical cyclization has enjoyed extensive success in the application to natural product synthesis.[13] Far and away, the best attributes of this method were the mild conditions, functional group tolerance, and wide array of radical precursors. For example, remote functional groups such as alcohols, amines, ketones, esters, ethers and chlorides were stable to the conditions. Precursors to carbon radicals that have been exploited include bromides, iodides, alkynes,

alkyl and aryl sulfides, alkyl and aryl selenides, and nitro groups. In terms of stereoselectivity, the most successful examples of free radical cyclization have usually contained a structural feature, such as a ring, that restricted the freedom of rotation of the alkene or the tether. This limitation was a result of the minimal alkene facial selectivity, or lack of conformational control, exhibited by an alkyl radical. Curran and Fraser-Reid have utilized this approach to solve quinane structural problems. Curran has prepared a number of angular,[14a] linear,[14b] and propellane[14c] triquinane natural products using a tandem cyclization approach, as illustrated for an intermediate to crinnipelin (eqn. 7).[14a] In this case, Curran took advantage of the kinetic propensity of the sequential alkyl radicals to react from the same face of the cyclopentane ring, thus controlling the relative stereochemistry of the ring fusion. Fraser-Reid has controlled the absolute stereochemistry by performing similar serial cyclizations (eqn. 8),[15a] in which the quinane precursor was secured to a chiral carbohydrate template. In this way, enantiomerically pure quinanes were produced.

24a; X = CH_2I 61% Yield 25a; Y = H, H
24b; X=COSePh 62% Yield 25b; Y = O

(7)



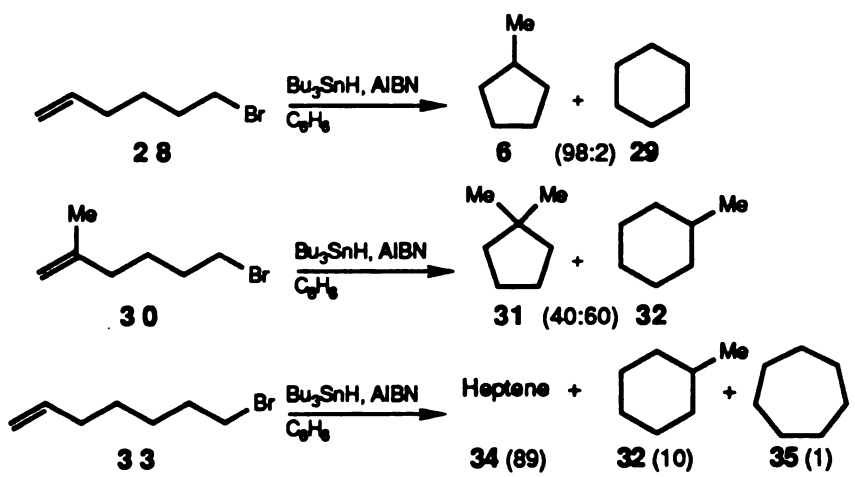
26 27

(8)

In the simplest case, radical cyclization was effective for selective carbon-carbon bond formation (Scheme 3).[13] For example, cyclization of **28** provided

a 98:2 ratio of *exo:endo* products. However, the regioselectivity of ring closure was dramatically reduced when a geminally disubstituted olefin (**30**) was employed. Thus, the important terpene element, the gem-dimethyl group, was not accessible *via* this route. Moreover, extention to six-membered rings via *exo* cyclization (**33**) has been a troublesome operation for entropic reasons, providing only 11% cyclization contaminated by a trace of the *endo* product as well.[16] In this case, the lifetime of the radical was too short for the significantly slower cyclization to occur prior to hydrogen-atom abstraction. For the sake of clarity, the rates of 5-*exo*-trig cyclization, six-*exo*-trig cyclization, and hydrogen atom transfer are, ($k=2x10^5$, 25 °C),[17] ($k=5x10^3$, 25 °C),[17] ($k=6x10^6$, 25 °C),[18] respectively, which help explain the different levels of success for the two reactions.

Scheme 3. Regioselectivity of Free Radical Cyclizations



Substrates which possessed an alkyl group on the tether suffered a lack of stereoselectivity for radical ring closure (Scheme 4).[19] The diastereoselectivities for bromides **36a-c** ranged from 2:1 to 4:1, with the major product arising by cyclization from the more stable chair conformation.[20]

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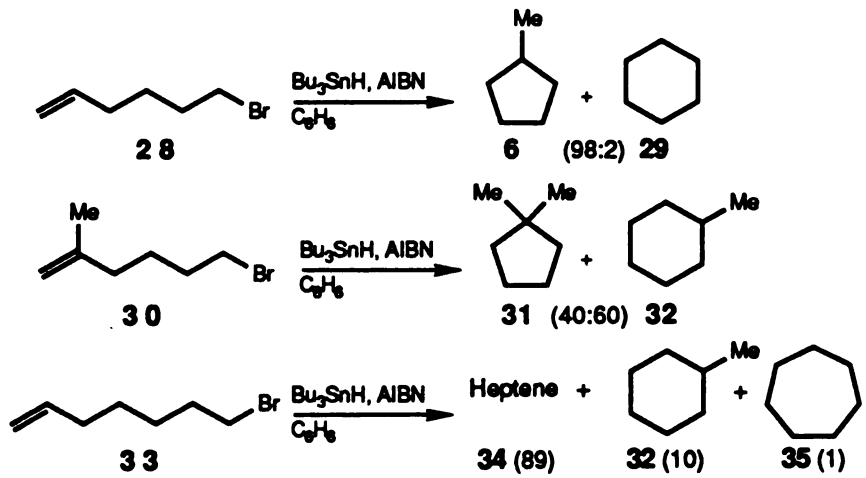

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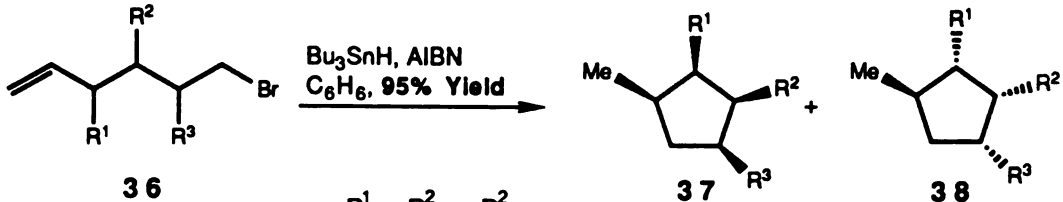
Scheme 4. Stereoselectivity of Free Radical Cyclizations



36 37 38

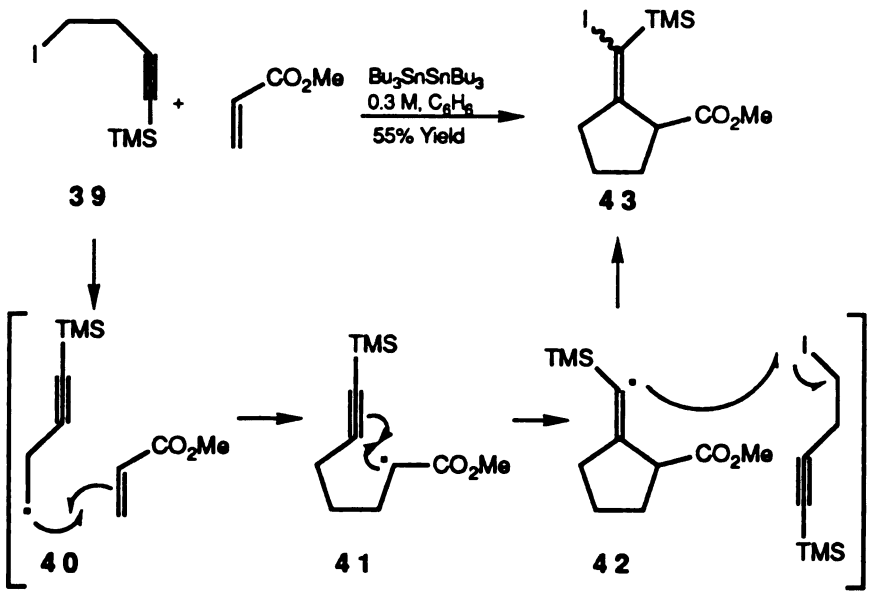
	R1	R2	R2	37	38
a:	Me	H	H	17	83
b:	H	Me	H	75	25
c:	H	H	Me	35	65

In their current form, radical cyclizations have practical and environmental limitations as well. In order to promote intramolecular events over hydrogen abstraction or dimerization, concentrations of <0.01 M were required. Industrial application of this technique would be costly and cumbersome in terms of solvent requirements, recovery or disposal of solvent, and the handling and disposal of the toxic tin byproducts.

The continued efforts of many researchers have increased the level of sophistication and applicability of free radical processes. As a result, "yesterday's limitations" are becoming obsolete. One major problem of the tin-hydride method was that substituents surrounding the radical had little effect on the rate of hydrogen-atom abstraction. Consequently, most alkyl radicals had similar lifetimes with respect to hydrogen-atom abstraction. For relatively slow cyclizations, such as 6-*exo*-trig cylizations, hydrogen abstraction becomes competitive with cyclization. Although not recognized at the time, a major synthetic breakthrough happened in 1948 when Kharasch discovered what is called today the "atom-transfer reaction".[21] This reaction delivers a C-X (X=halogen) bond across a double or a triple bond. The attractive feature of this reaction was that it was devoid of a hydrogen atom donor. Consequently, longer lifetimes of the incipient radicals were permitted without interception by a hydrogen-atom donor, which in turn allowed for slower inter- or intramolecular

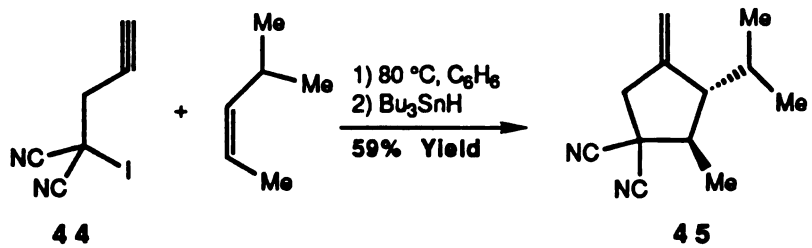
events to occur. Finally, predictable and efficient five-, six-, or seven-membered ring formation at a reasonable concentration (0.3 M) was at last a viable option through radical methodology.[22]

Scheme 5. A Possible Propagation Sequence for the Atom Transfer Reaction



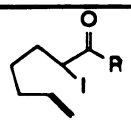
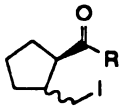
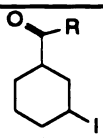
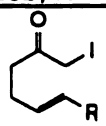
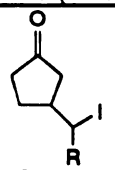
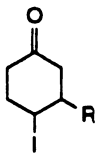
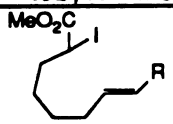
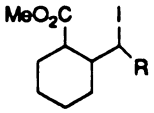
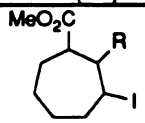
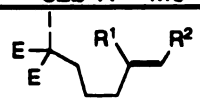
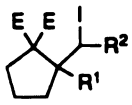
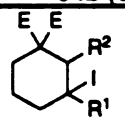
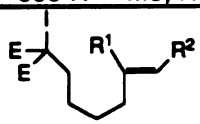
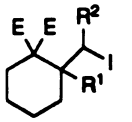
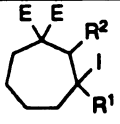
Curran has developed a number of new strategies based on the atom transfer principle. For example, a formal [3+2] annulation procedure was designed that began by treating alkyliodide **39** with hexabutylditin and light in the presence of an activated olefin (Scheme 5).[23] The initial radical formed (**40**) added to the olefin in a Michael fashion which produced **41**, followed by an intramolecular 5-*exo*-dig cyclization. The resulting vinyl radical **42**, which was less stable than the preceding ones, underwent iodine atom transfer from the starting iodide which produced **43** and completed the chain process. The key ingredients to the successful design of this procedure were the delicate balance between the relative strength of the carbon-iodide bond, and the reactivity of the carbon radicals along the way. An illustrative example was the

divergent behavior of **44** with 4-methyl-2-pentene (eqn. 9) compared to that shown in Scheme 5. In this case, a two-step sequence was necessitated. In the first step, the intermolecular atom transfer addition across the olefin could be thermally promoted in the absence of the tin reagent, owing to the more labile carbon-iodide bond, which provided a single regioisomer. This reaction produced no trace of cyclized products, only the acyclic secondary alkyl iodide. The greater reactivity of the 2° alkyl radical compared to the stabilized radical **41** coupled with the weaker carbon-iodide bond, resulted in premature iodide atom transfer. Treatment of the 2° iodide with Bu_3SnH yielded a single regio- and stereoisomer, methylenecyclopentane **45**.



44 **45** (9)

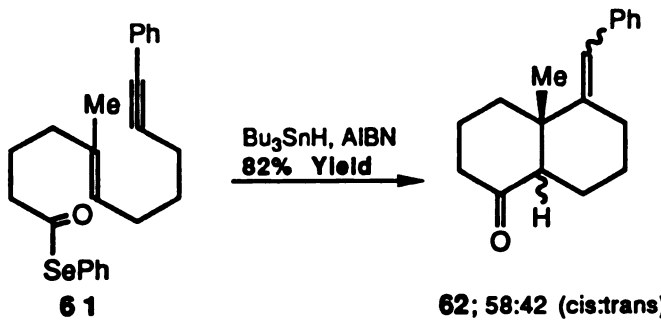
Table 1. Regioselectivity of Atom Transfer Reactions

Substrate	Products		Yield
	EXO (cis/trans)	*ENDO* (cis/trans)	
			
46a; R = OMe	**47a** (53/40)	**48a** (3/4)	83
46b; R = Ph	**47b** (21/54)	**48b**(8/17)	68
			
49a; R = H	**50a** (<3)	**51a** (>97)	56
49b; R = Me	**50b** (25)	**51b** (75)	73
			
52a R = H	**53a** (48/32)	**54a** (15/5)	68
52b R = Me	**53b** (50/50)	**54b** (0)	60
			
E=CO_2Et			
55a R^1 = H; R^2 = H	**56a** (90)	**57a** (10)	86
55b R^1 = H; R^2 = Me	**56b** (10)	**57b** (0)	84
55c R^1= Me; R^2 = H	**56c** (100)	**57c** (100)	84
			
E=CO_2Et			
58a R^1 = H; R^2 = H	**59a** (60)	**60a** (40)	66
58b R^1 = H; R^2 = Me	**59b** (10)	**60b** (0)	62
58c R^1= Me; R^2 = H	**59c** (100)	**60c** (100)	71

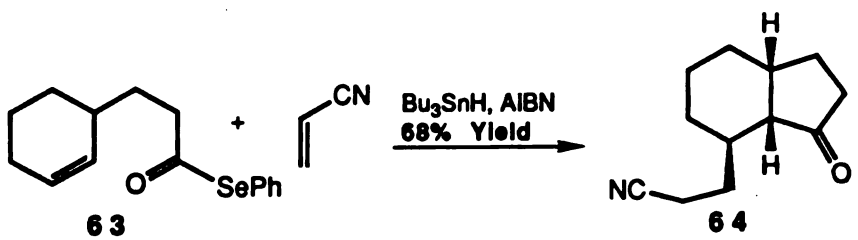
The results in Table 1 established guidelines for application of atom transfer reactions to larger rings.[22] Treatment of **46a** under the atom transfer conditions resulted in excellent regiocontrol (93:7, **47a:48a**) favoring 5-*exo* over 6-*endo* cyclization. A reversal in the mode of cyclization could be brought about by placing the carbonyl on the interior of the forming ring (see **49**). In this case, *endo* cyclization was the dominant pathway (3:97, **50a:51a**). Calculations have shown that the product of this cyclization, like all other intramolecular free radical reactions, was the kinetic product. The transition state for this cyclization resembled that of the [3,3] reaction. Cyclization of **52a** resulted in more *endo* cyclization than for the cyclization of **46**. This mode could be suppressed by incorporation of a terminal alkyl group on the olefin (**52b**). Curran has also developed atom-transfer cyclizations based on iodomalonates. Cyclization of **55a** and **58a** demonstrated that for a terminal alkene, irrespective of tether length, a mixture of *exo* and *endo* products were formed. Each of these modes could be controlled and amplified by situating an alkyl group on the interior (see **55b** and **58b**) or on the exterior (see **55c** and **58c**) of the olefin. Although these examples extend the applicability of radical cyclization, control of simple diastereoselectivity remains a hurdle to overcome.

Boger[25] has recently described a new modification for free radical cyclization, which featured an acyl radical. Acyl radicals were shown to effectively participate in tandem intramolecular reactions as well as intramolecular-intermolecular and intermolecular-intramolecular sequences. Treatment of **61** (eqn. 10) with the standard tin hydride conditions preceded with initial 6-*endo*-trig cyclization, followed by a rapid 6-*exo*-dig cyclization. The initial radical ring closure was consistent with Curran's results for a substrate that possessed a carbonyl on the interior of the forming ring. However, Boger maintained that *endo* cyclization was merely a result of the kinetic deceleration

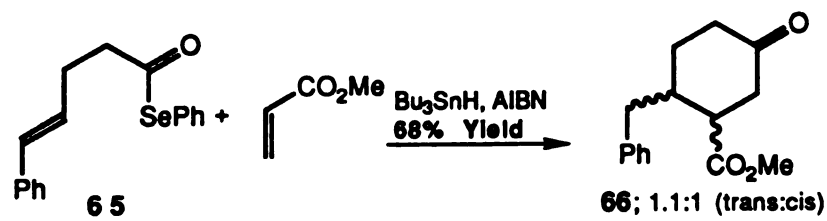
of the 5-*exo* mode due to the flanking methyl group on the olefin. Although the regiocontrol was excellent in this case, the minimal stereoselectivity at the ring junction was a serious concern. Attempted epimerization of **62** resulted in only a slight increase for the trans fusion. The 5-*exo*-trig cyclization of **63** (eqn. 11) was very stereoselective, as expected for a rigid system. A more impressive result was the efficiency and stereocontrol of the subsequent intermolecular Michael addition of the resultant 2° radical; only a single stereoisomer of **64** was produced. Treatment of **65** (eqn. 12) under the radical conditions, illustrated that the acyl radical bypassed the 4-*exo* and the 5-*endo* intramolecular pathways to participate in a regioselective addition to methyl acrylate. The stabilized radical that resulted underwent a 6-*exo*-trig cyclization to produce **66** (1.1:1) to complete this formal [4+2] annulation sequence.



61 **62**; 58:42 (cis:trans) (10)



63 **64** (11)



65 **66**; 1.1:1 (trans:cis) (12)

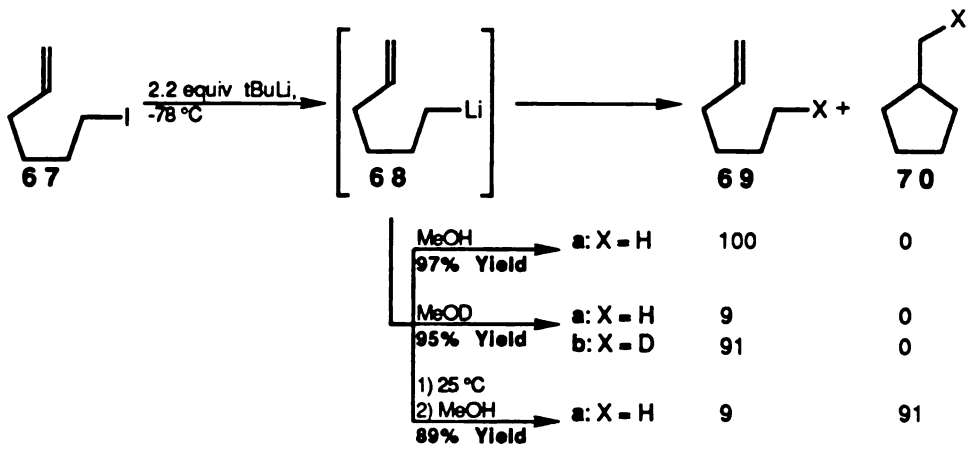
A number of new and exciting topics in free radical chemistry include macrocyclizations[26] and "chiral radicals".[27] Using their respective methods, Boger, Curran, and Porter have have produced macrocycles with ring sizes as large as 20 members in surprisingly high yields. Chiral auxiliaries have shown promise for induction of enantioselective bond formation for both intramolecular cyclizations, and for the acyclic stereocontrolled addition of radicals to electron deficient olefins. All of these new developments in free radical chemistry have greatly expanded the repertoire of bond forming reactions available to the synthetic chemist.

C. Lithium-Mediated Cyclizations

Cyclization methods based on alkyllithiums have received considerable attention on a number of fronts, including synthetic and mechanistic fronts. Product analysis for the isomerization of 5-hexen-1-yllithium has been used as a probe for determining whether cyclization proceeds *via* an anionic mechanism[28] or by single electron transfer.[29] If nothing else, the debate which ensued between Bailey (anionic) and Ashby (single electron transfer) has made for some interesting reading. Suffice it to say that there is compelling evidence to support each claim[28] depending on the alkyl halide (1°, 2°, or 3°), the nature of the halogen (I, Br, Cl), and the method used to generate the alkyllithium. A number of features of this method are synthetically attractive. First, the requisite alkyllithium could be generated by numerous methods, including (1) lithium-halogen exchange,[30a] (2) lithium-tin exchange,[30b] (3) Shapiro degradation of tosylhydrazones,[30c] and (4) electrochemical reduction of carbon-halogen[30d] or carbon-carbon bonds.[30e] Secondly, cyclization of a variety of substituted 5-hexen-1-yl systems demonstrated complete regiospecificity,[30a] *exo* addition,

along with excellent and predictable stereoselectivities.[31] Finally, the post-cyclization alkyllithium could be functionalized with a variety of electrophiles, providing useful functionality for further elaboration.[28,30a,30c]

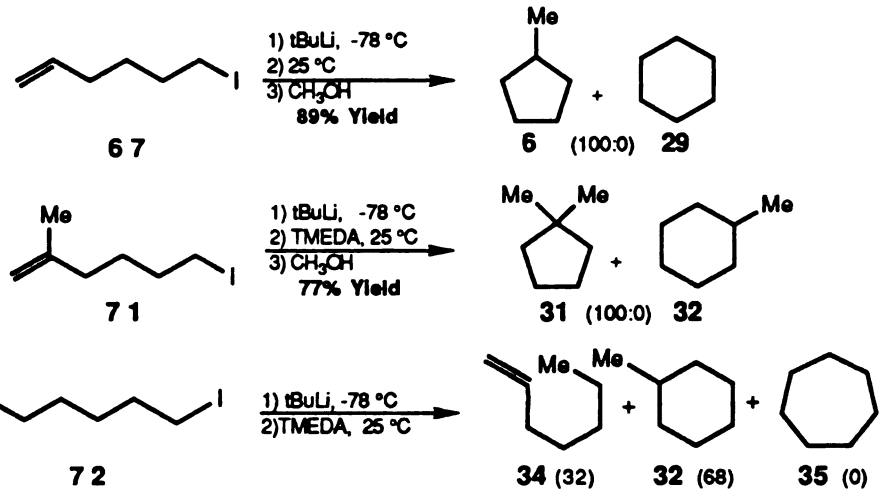
Scheme 6. Evidence for Proton Abstraction



Treatment of iodide **67** with 2.2 equiv of t-BuLi at -78 °C led to clean generation of the alkyllithium **68** (Scheme 6).[30a] This species was stable indefinitely at -78 °C. Also, upon quenching the reaction mixture at -78 °C with CH_3OH, no detectable amount of methylcyclopentane was observed. However, quenching the reaction mixture with CH_3OD, resulted in a 95% yield of **69a-b** and only 91% deuterium incorporation (**69b**). Thus, only an 87% yield of the alkyllithium was actually present. These results outline the fundamental limitation of this method, extreme reactivity of the alkyllithium, in which the most obvious consequences were reduced cyclization yields and eventual separation problems. Two possible explanations have been set forth for the low yields of alkyllithium formation: (1) the organolithium generated abstracted a proton from the t-butyl iodide formed *in situ*, competitively with the second equivalent of t-BuLi and/or (2) proton abstraction from the diethyl ether occurred.[28] In either case, the extreme reactivity demonstrated by the

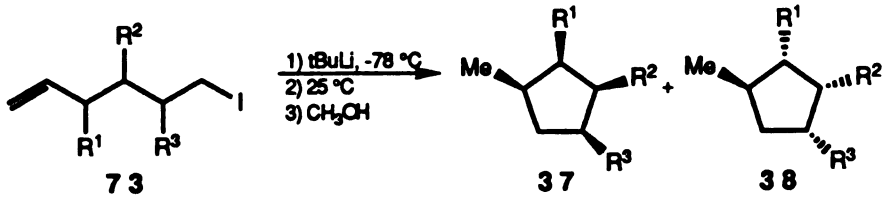
alkyllithium minimized the potential functional groups that could be present. Diminishing the amount of diethyl ether with an equal increase in the pentane concentration has been shown recently to be marginally effective in reducing the amount of substrate reduction.[32] Withstanding these drawbacks, warming **68** to ambient temperature caused rapid and selective methylcyclopentane formation. The activation parameters for this isomerization have been determined to be $\Delta H = 11.8 \pm 0.5$ kcal/mol and $\Delta S = -30 \pm 2$ eu, which reflects the importance of temperature.[30a] Treatment of **72** under the same conditions, produced only 6% methylcyclohexane (Scheme 7). However, with the use of a complexant such as TMEDA, the extent of 6-*exo*-trig cyclization was increased to 68%. The role of the Lewis base served to lengthen, and thus weaken, the carbon-lithium bond. This, in turn, accelerated cyclization to the point of becoming competitive with proton abstraction. Substrates which possessed geminal substitution on the olefin (**71**) also required the use of Lewis bases to accelerate the sluggish reaction. The result was the regioselective formation of **31**. It is important to note the marked difference in selectivity between lithium cyclization of **71**, and the analogous cyclization of **30** by radical methods (Scheme 3). Acyclic compounds with vicinal substitution on the olefin failed to cyclize under any conditions.

Scheme 7. Regioselectivity of Alkyllithium Cyclizations



Cyclization of **73a-c** provided the opportunity to probe the stereochemical aspects of the reaction (Scheme 8).[31] Cyclization in the absence of any additives produced excellent diastereoselectivities in all cases. If PMDTA was present in the reaction, a noticeable increase in stereoselectivity was achieved. The enhanced selectivity was attributed to the lower temperatures needed for cyclization in the presence of PMDTA.

Scheme 8. Stereoselectivity of Alkyllithium Cyclizations

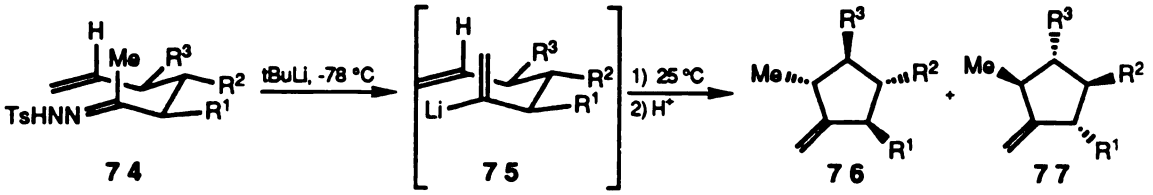


Additives	Yield		R^1	R^2	R^3		
none/PMDTA	79/81	a:	Me	Me	Me	8/8	92/97
none/PMDTA	98/88	b:	H	H	H	90/94	10/6
none/PMDTA	83/73	c:	H	H	H	9/3	91/97

Chamberlin has examined the stereoselectivities of a related process, in which a vinyllithium species was cyclized (Scheme 9).[30c] Treatment of tosylhydrazones **74a-c** with t-BuLi (2.2 equiv) served to generate vinyllithium

species **75a-c**. Upon warming these compounds to ambient temperature, high yields and stereoselectivities were noted. As with other 5-*exo*-trig cyclizations, the relative configuration of the newly formed asymmetric center could be predicted by invoking a chair transition state, wherein the alkyl groups occupied pseudo equatorial positions.

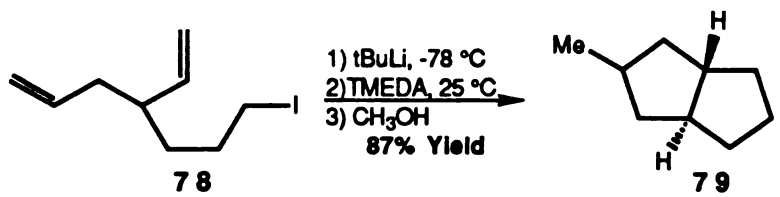
Scheme 9. Stereoselectivity of Vinyllithium Cyclizations



	R1	R2	R3	Yield	76	77
a:	Me	H	H	70	17	83
b:	H	Me	H	65	91	9
c:	H	H	Me	70	9	91

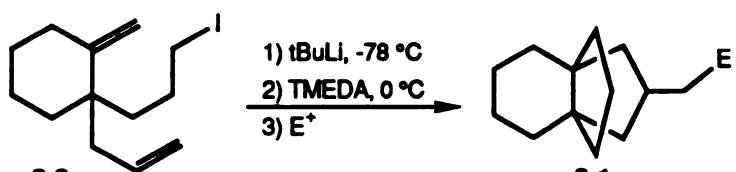
Bailey has performed calculations for the transition state of the lithium cyclization.[31] Molecular mechanics and *ab initio* calculations arrived at an energy minimum where the acyclic alkenyllithium was in a pseudo chair conformation, not a linear array of atoms, and that this conformation represented an intermediate. These calculations revealed that contributing to the stabilization of this intermediate was the coordination of the lithium to the carbon-carbon π bond, which was first suggested by Oliver in 1966.[33] This stabilization would be maximized when the carbon-lithium bond was *syn*-coplanar to the olefin. This interaction between lithium and the olefin could contribute to the alkene facial selectivity observed for lithium mediated cyclizations. These calculations were qualitatively consistent with experimental facts and help to ascertain the discrepancy in stereocontrol with its radical counterpart (a radical would not be expected to interact with a π bond). Substrates **73b** and **73c** illustrate that cyclization was under kinetic control.

Both substrates gave rise to 1,3-dimethylcyclopentanes, yet were highly selective for different isomers. Further proof was evident in the tandem cyclization of **78** (eqn. 13),[34] which produced the thermodynamically less stable *trans*-[3.3.0] bicyclooctane (the cis isomer is 6.4 kcal/mol more stable). In contrast, radical cyclization of the corresponding bromide produced multiple products in which the trans isomer was present as <4% of the mixture.[35]



78 **79** (13)

Finally, cyclization of **80** (eqn. 14) produced in high yields the [4.3.3] propellane skeleton.[36] More importantly, it serves to further illustrate the adaptability of this method to complex ring patterns and that the final alkyllithium was sufficiently stable to take part in useful, high yielding intermolecular events with CO_2, aldehydes, and activated alkyl halides.



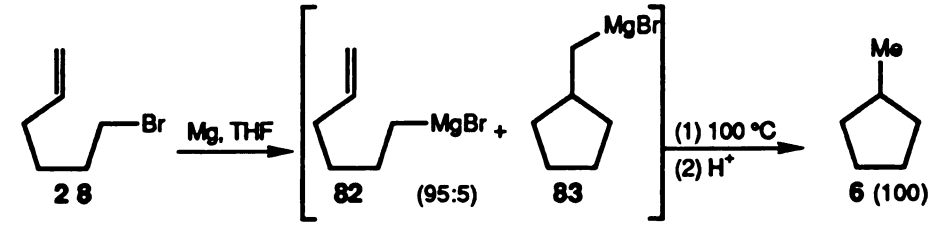
80 **81** (14)

a: $E^+ = CH_3OH$ — a: E = H; **81% Yield**
b: $E^+ = CO_2$ — b: E = CO_2H; **60% Yield**
c: E^+ = PhCHO — c: E = $PhCH_2OH$; **80% Yield**
d: $E^+ = CH_2CHCH_2Br$ — d: E = CH_2CHCH_2; **82% Yield**

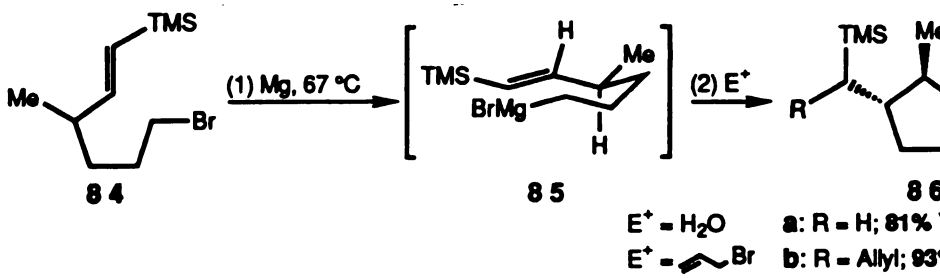
D. Magnesium-Mediated Cyclizations

Grignard reagents have shown little tendency toward addition to olefins in intermolecular reactions. However, when **28** was added to magnesium in diethyl ether or THF and the products hydrolyzed, the resulting mixture

consisted of a 95:5 ratio of **82** and **83** respectively (eqn. 15).[37] Formation of **83** was suggested to arise from radical intermediates generated by single electron transfer (SET) during the formation of the Grignard reagent. When the reaction mixture was heated in excess of 100 °C, complete conversion to **83** resulted.[38] Richey studied the rates of reaction and the simple diastereoselectivity of some substituted 5-hexen-1-yl and 6-hepten-1-ylmagnesium bromides. As expected, five-membered ring formation was faster than that of the six-membered ring (by a factor of 2800). The diastereoselectivity was modest, favoring cyclization from the more stable chair conformation. Utimoto incorporated a trimethylsilyl group on the terminal carbon of the olefin to accelerate the cyclization and reduce the necessary reaction temperatures (eqn. 16).[39] Thus, treatment of **84** with 1.5 equivalents of magnesium in THF at 67 °C to provided, upon quenching, **86a** as the only product. Moreover, when cyclization was complete, trapping the final Grignard intermediate could be achieved with suitable electrophiles.



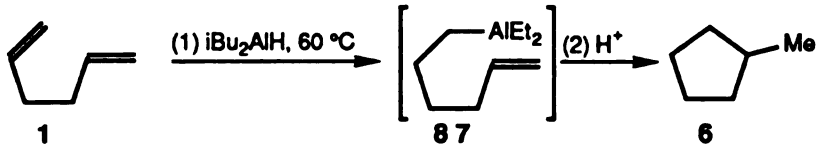
(15)



(16)

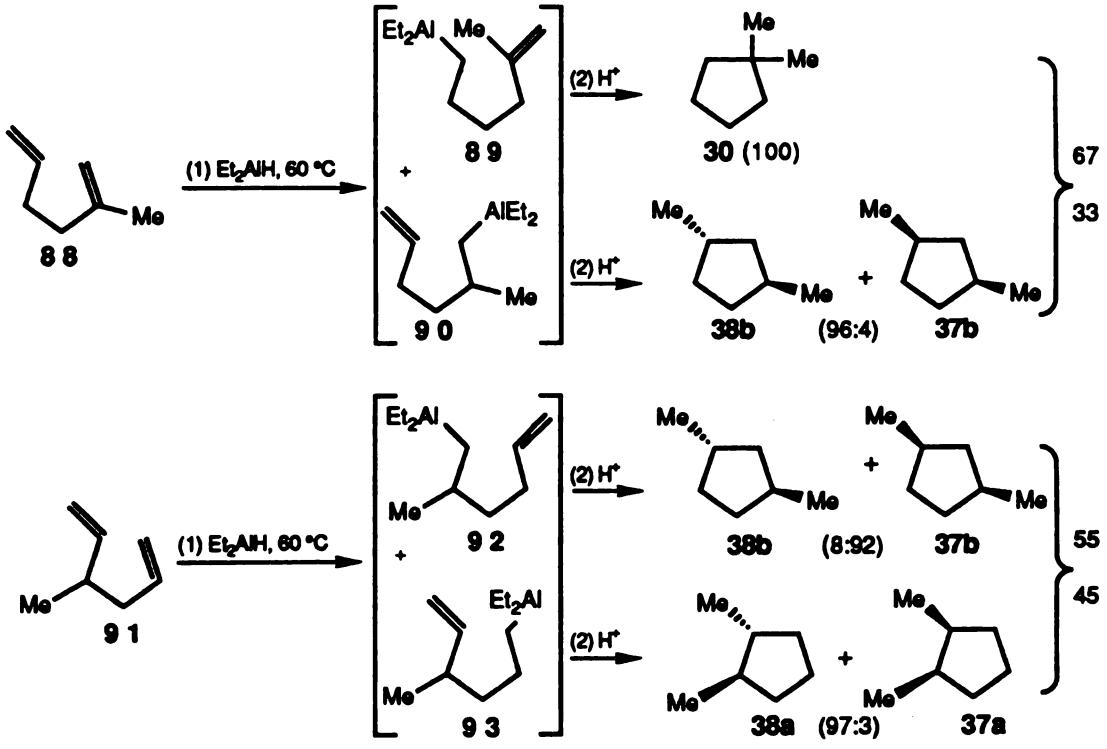
E. Aluminum-Mediated Cyclizations

Alkyl aluminum hydrides have received limited attention as a method to convert 1,5-dienes into methylcyclopentanes. Although, when 1,5-hexadiene (**1**) was treated with 2.1 equivalents of iBu_2AlH at 60 °C for 16 hours (eqn. 17), methylcyclopentane (**6**) accounted for >98% of the products formed, after hydrolysis, with the balance of material being n-hexane.[40] However, when 1,6-heptadiene was treated under the same conditions, less than 1% of the product mixture was methylcyclohexane with the major component n-heptane (>99%).



(17)

Scheme 10. Stereoselectivity of Aluminum Cyclizations

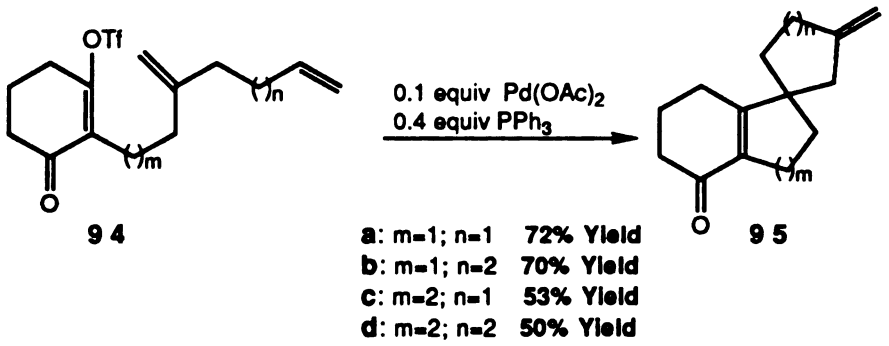


In an attempt to answer some of the questions about the stereoregulating forces present in the Ziegler-Natta polymerization of olefins, Stefani investigated the diastereoselectivity for the aluminum-mediated cyclizations of **88** and **91** (Scheme 10).[40] Reaction of **88** and **91** with Et_2AlH produced two structural isomers in each case (**89**,**90** and **92**,**93** respectively), due to the indiscriminate addition of the alkylaluminum hydride to the dienes. Cyclization and analysis of the reaction mixtures revealed important selectivity information. For all cases, only *exo* insertion was observed, even for the geminally substituted olefin, **89**. The most important feature of the reaction was the ability of the alkylaluminum to control the relative configuration of the newly formed asymmetric center. Selectivities for the cyclization of **90**, **92**, and **93**, ranged from 92:8 to 97:3. These results, which paralleled those of lithium cyclizations, reflect the ability of both lithium and aluminum to coordinate the olefin and thus control the facial selectivity of olefin insertion and the equatorial deployment of methyl groups.

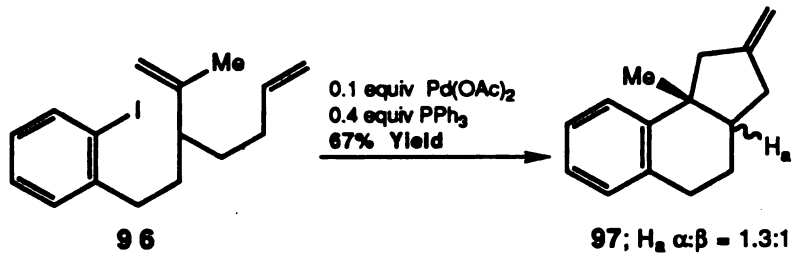
F. Palladium-Mediated Cyclizations

Transition metals are particularly well-suited for this type of bond construction because of their ability to insert olefins into carbon-metal bonds. Palladium remains a convenient metal to use (despite the expensive cost) because of the variety of ways it can be introduced into the cyclization substrate and because catalytic processes are possible. Palladium can be bound to carbon by either transmetallation or through oxidative addition into a carbon-heteroatom bond. Overman has recently reported tandem cyclizations using palladium, generating polycyclic molecules with spiro (eqn. 18)[41a] or fused rings (eqn. 19).[41b] The catalytic cycle for these cyclizations consisted of

oxidative addition of Pd(0) (generated *in situ*) into the carbon-triflate or the carbon-iodide bond, sequential intramolecular olefin insertions, β-hydride elimination, and reductive elimination of H-X (X=heteroatom) from palladium which regenerated the Pd(0) catalyst. Olefin insertion usually followed in an *exo* manner to yield the smaller ring, unless some dominating steric factor directed *endo* insertion. The major limitation of this methodolgy was that the initial carbon-palladium bond must either contain an aryl or a vinyl carbon to prevent ß-hydride elimination prior to cyclization.



94 95 (18)



96 97; H_a α:β = 1.3:1 (19)

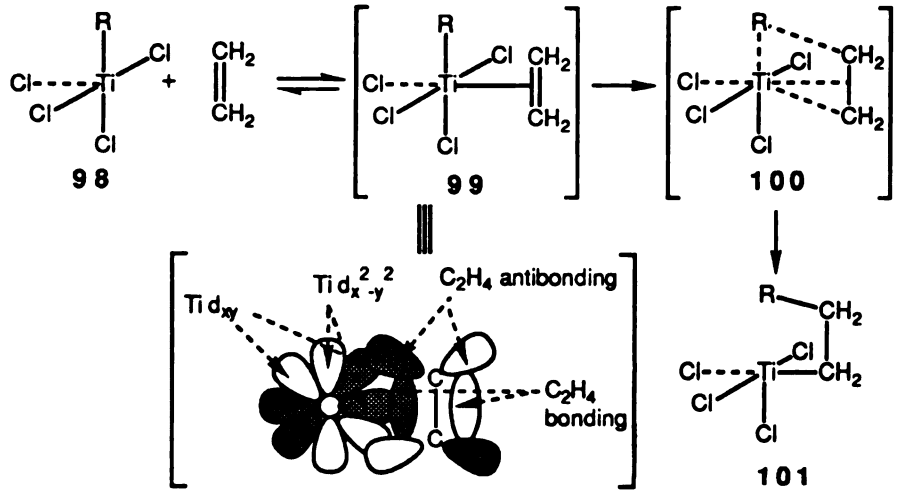
3. Background for the Mechanism of Ziegler-Natta Polymerization

Ziegler-Natta polymerization remains one of the most important industrial processes. Due to the vivid imaginations of a number of polymer chemists, extensive knowlege exists on how to control catalyst activity and the tacticity (stereochemistry) of the polymer, be it isotactic[42] or syndiotactic.[43] However, very little is actually known about the fundamental steps that comprise the

mechanism. Central to the controversy was the interaction of the olefin with the metal, mode of insertion, and how these factors influenced the stereochemistry of each insertion. Of the plethora of mechanisms that have come and gone, two have received serious consideration, the first by Cossee[44] and the other by the combined efforts of Green and Rooney.[45] Proof of the credibility of these proposals can be seen by the enduring efforts to substantiate and/or disprove these mechanistic possibilities.

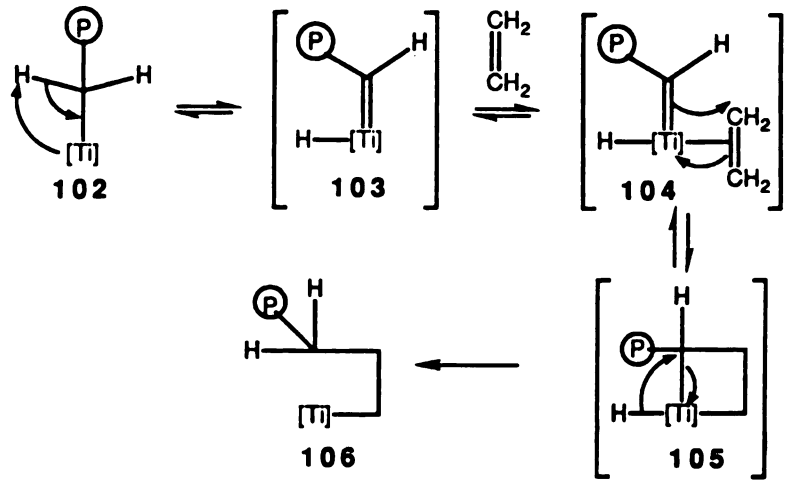
Cossee suggested, in 1960, a direct insertion mechanism, the details of which are shown in Scheme 11.[44] Compound **98** (shown only for the monomer, yet the dashed titanium-chloride bond indicates the point of attachment of another monomer) was suggested to result from the treatment of $TiCl_3$ with an alkyl aluminum compound. Reaction of **98** with ethylene generated complex **99** wherein the olefin interacted with the available d orbitals of the titanium to form a π complex. Cossee reasoned that **99** was a credible structure based on a similar finding by Chatt and Duncanson,[46] in which a crystal structure revealed that a platinum complex bound an olefin in this manner. The σ bond between the olefin and titanium was formed through the interaction of the π electrons of the olefin with the $d_{x^2-y^2}$ orbitals of the metal.[44,47] Further stabilization could be provided by interaction of the d_{xy} orbital and the antibonding orbitals of the olefin. Propagation was proposed to occur *via* a four centered transition state, **100**, which yielded **101** after insertion.[48]

Scheme 11. The Cossee-Arlmann Mechanism for Chain Propagation



Green and Rooney discounted mechanisms such as Cossee's, which involved direct insertion.[45] They did so on the grounds that isolable alkyl-metal-olefin complexes (metal=W or Mo) could not be induced to insert the alkyl group. On the other hand, similar hydrogen-metal-olefin complexes readily inserted the hydrogen into the olefin. It has also been shown that certain olefin polymerization catalysts could participate in ring-opening metathesis reactions. All of these facts were combined to give rise to their mechanistic proposal (Scheme 12), which differed from all others by the presence of a metallocyclobutane intermediate (**105**). Thus, α-hydrogen elimination of **102** (the net result being oxidation of the metal) produced metallocarbene **103** which was proposed to complex the olefin to give rise to **104**. A [2+2] reorganization of the π electrons could form the metallocyclobutane **105** as the key intermediate. The propagation sequence was completed by a 1,2-hydride shift resulting in **106** (and return to the initial oxidation state of the metal).

Scheme 12. The Green-Rooney Mechanism for Chain Propagation



The lack of conclusive experimental evidence for these mechanisms has prompted a number of different investigations. One path toward obtaining such evidence involved synthesizing isolable metal complexes that resembled proposed intermediates, and the second, which will be addressed shortly, involved monitoring the stereochemical details of a single olefin insertion to probe the microstructure of these intermediates. There have recently been a number of reports of alkyl-metal complexes in which hydrogens on the alkyl chain were suggestively close to the metal center, implying a bonding interaction to the metal. Representative examples of these "agostic hydrogen interactions" are shown in Figures 1-3, in which the only difference was whether an α- or a β-hydrogen participated. Green suggested that the α-hydrogen interaction in Figure 1 lent support and resembled his propagation mechanism.[49] In contrast, β-hydrogen interaction (Figures 2[50a] and 3[50b]) was proposed to represent a termination intermediate, namely that of β-hydride elimination. A similar claim has been set forth for a zirconocene polymerization catalyst.[42a]

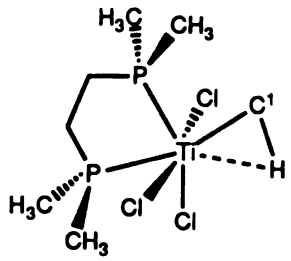


Figure 1. α-Agostic Interaction for **107**: Ti-C^1-H = 70°; Ti-H = 2.03 Å.

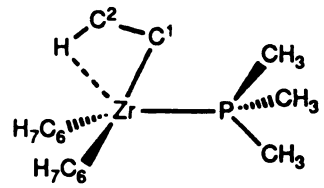


Figure 2. β-Agostic Interaction for **108**: Zr-C^1-C^2 = 85°; Zr-H = 2.16 Å.

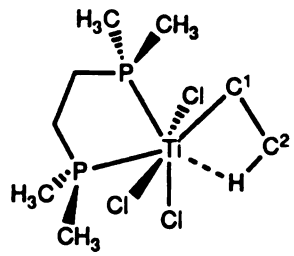


Figure 3. β-Agostic Interaction for **109**: Ti-C^1-C^2 = 86°; Ti-H = 2.29 Å.

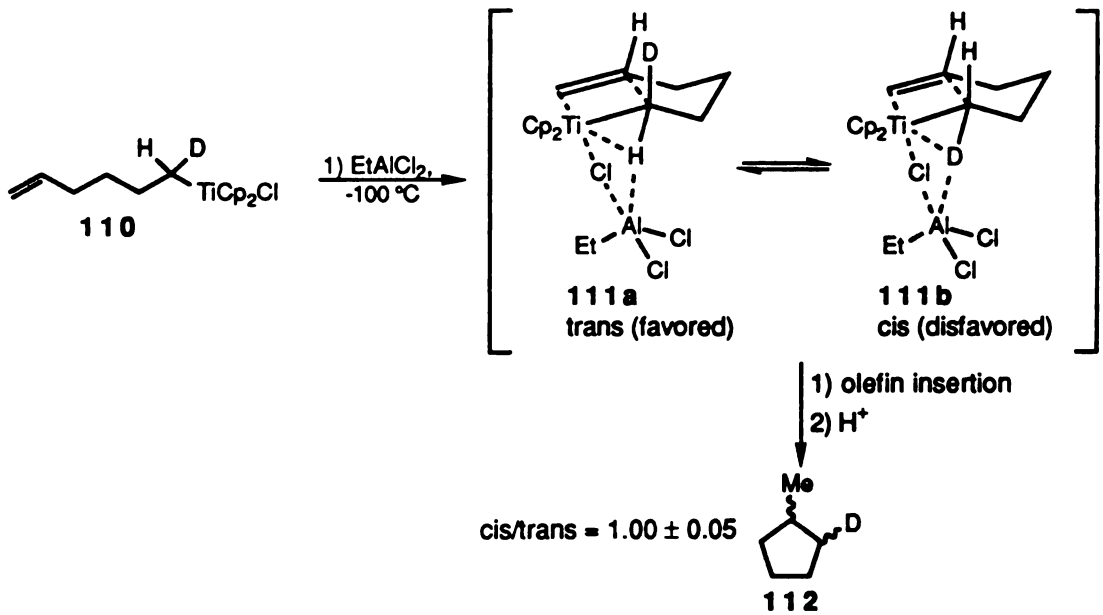
Two major problems were apparent with the foundation of the mechanism of Green and Rooney. First, the fact that the complexes of tungsten and molybdenum did not insert an alkyl group should have not been surprising at all. These complexes were electron rich, 18 electron complexes, which is in direct contrast to typical, active Ziegler-Natta catalysts (primarily 14-16 electron complexes). Secondly, a more serious problem was illustrated in Figures 2 and 3. These figures demonstrated that when α- and β-hydrogens were present, as in the growing polymer chain, β-agostic interactions dominate over α-interactions. Unless α- and β-hydrogen interactions are in equilibrium in solution, it is unclear, based on the experimental facts and their conjecture, how polyolefins would be produced. In fact, β-hydrogen interactions have been suggested to play a role in polymerization,[48,50a,51] although the cursory role has not explicitly been determined.

The role of β-agostic hydrogens is complex. Brookhart has shown that a cationic ethylcobalt(III) complex adopts a β-agostic structure.[51] Treatment of this cobalt complex with three equivalents of ethylene in an NMR tube resulted in sequential oligomers of ethylene. However, the first insertion was markedly slower than subsequent insertions. Brookhart attributed this rate difference to the unfavorable disturbance of the β-hydrogen interaction (9.2 kcal/mol), which was contributing electronic stabilization to the electron deficient metal center. After the initial insertion, other agostic interactions were observed by NMR analysis. Independent synthesis and NMR analysis of a terminally bound cationic butylcobalt(III) complex, with a distinguishable β-hydrogen agostic interaction, provided direct correlation to that observed after the first insertion of ethylene. Based on these results, Brookhart contended that alkyl migration was the rate limiting step, and the agostic interaction played an undetermined subordinate role. Bercaw has observed similar results for a scandium complex.[48] For example, ethylene insertion was found to be faster for those alkylscandium complexes that did not contain a β-agostic hydrogen than those that did. Bercaw rationalized this phenomenon in which he proposed that β-agostic interactions represented ground state structures, and α-agostic interactions represented transition states for chain propagation. Jordan has suggested that the role of β-agostic interactions may be to influence the conformation of the β-carbon, and thus play a role in the stereoselectivity of α-olefin insertion.[50a]

Grubbs designed a clever experiment to test the Green and Rooney mechanism.[9a] To simplify the analysis, a system was choosen that would allow for only a single insertion to take place (Scheme 13). Central to the design was the the incorporation of an α-deuteron atom and an α-hydrogen (**110**). Grubbs reasoned that if α-activation was important, there would be an unequal

partitioning between the diastereomeric transition states (**111a** and **111b**) based on the relative strengths of the C-H and C-D bonds. Thus, if α-activation was pivotal in the insertion process, an excess of the trans product should be produced. Experimentally, Grubbs determined that, upon activation of **110** with $EtAlCl_2$, a 1:1 ratio of diastereomers was produced, which provided convincing evidence against the Green and Rooney mechanism. Grubbs proceeded to point out that "...polymerization is the chemistry of carbon-metal single bonds and metathesis is the chemistry of carbon-metal double bonds."[9a] Furthermore, Grubbs suggested that these findings supported the Cossee mechanism.

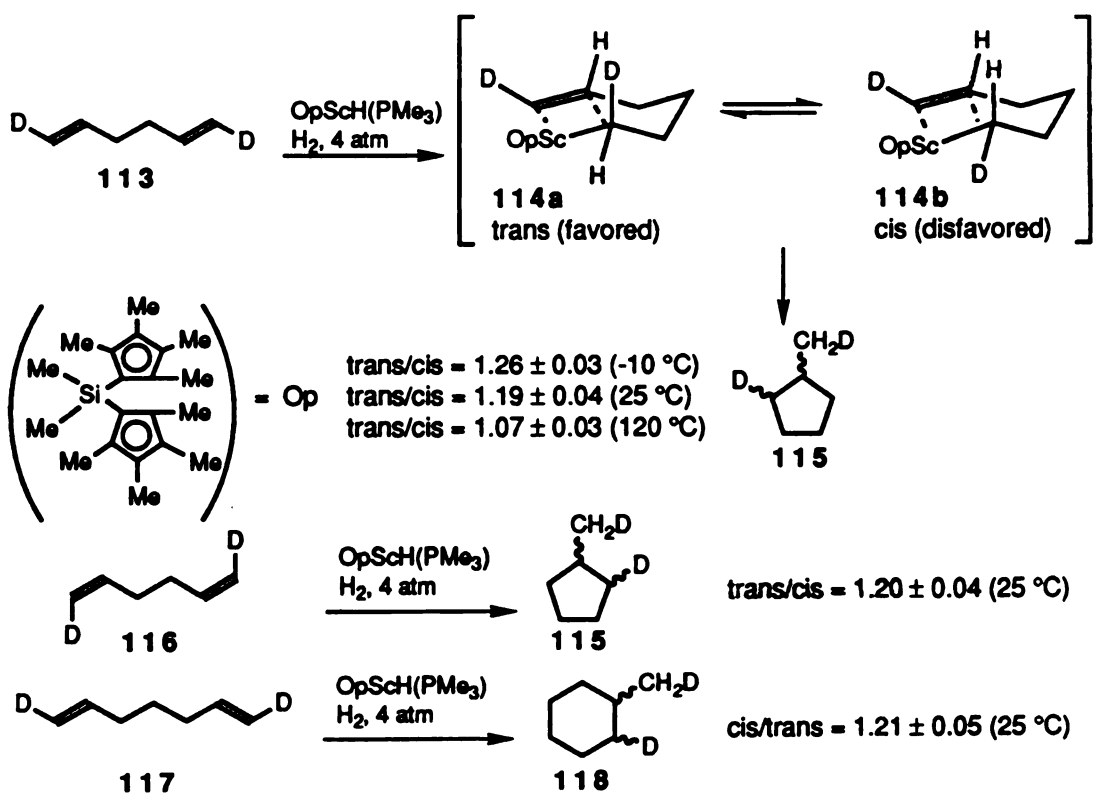
Scheme 13. Grubbs' Test for α-Hydrogen Activation



In contrast to the findings of Grubbs, Bercaw recently has shown that a scandium complex (isoelectronic with the Grubbs' complex) did in fact show an α-agostic assistance.[9c] Treatment of **113** with a scandium-hydride complex resulted in a regioselective production of **114** (Scheme 14). Cyclization of this complex provided an excess of the trans product. Moreover, the deuterium

isotope effect measured correlated in a normal enthalpic manner with respect to temperature. In order to insure that these results were not a consequence of sterics, based on the olefin geometry and the size of a deuterium atom versus a hydrogen atom, the cis olefins (**116**) were reacted under the same conditions. Consistent with the trans olefins, a deuterium isotope effect of the same magnitude was observed. Bercaw also noted α-activation for the cyclization of 6-hepten-1-ylscandium complexes generated from **117**. These results, coupled with Grubbs' findings, suggest that not all olefin polymerization catalysts proceeded through the same mechanistic pathways.

Scheme 14. Bercaw's Test for α-Hydrogen Activation



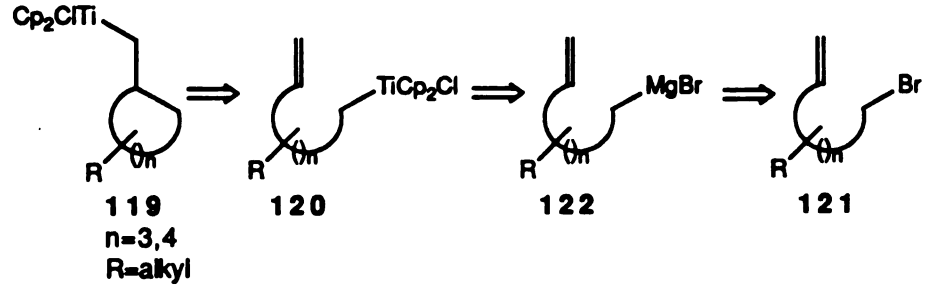
CHAPTER 1.

SYNTHESIS OF CYCLIZATION PRECURSOR SUBSTRATES AND STANDARDS

1. Introduction

The following chapters discuss the regio- and stereoselective features, along with mechanistic considerations for the transformation of **120** to **119** (Scheme 15). The antithetic sequence indicates alkenyltitanocene chlorides **120** as common intermediates in each reaction. Substrates analogous to **120**, differing in tether length and location of an alkyl group (R), were prepared by existing methodology[6] *via* Grignard reagent **122**, which could be prepared from alkyl bromides **121**. The present chapter will describe the synthetic routes for the preparation of the cyclization precursors (**121**) to be used in our various studies.

Scheme 15. Retrosynthetic Analysis of the Titanocene Dichloride-Mediated Carbocyclization

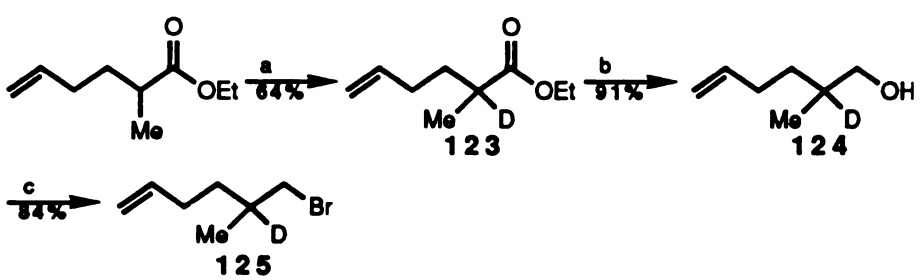


119 n=3,4 R=alkyl **120** **122** **121**

2. Synthesis of Five-Membered Ring Precursor Substrates

The synthetic sequence followed for the preparation of compound **125**, needed for our mechanistic study, is shown in Scheme 16. Beginning from the known α-methyl ester,[19] reaction with LDA at -78 °C generated the ester enolate. In order to remove acidic protons from the reaction mixture (i.e. DIPA), 1.25 eq nBuLi was added. The reaction was quenched with an excess of D_2O, which provided the α-methyl-α-deuterioester (**123**) in modest yield (64% yield). Subsequent treatment of **123** with LAH provided alcohol **124** (91% yield), which was converted to bromide **125** (84% yield) by the combined action of NBS and PPh_3.[52]

Scheme 16. Synthetic Route to 125

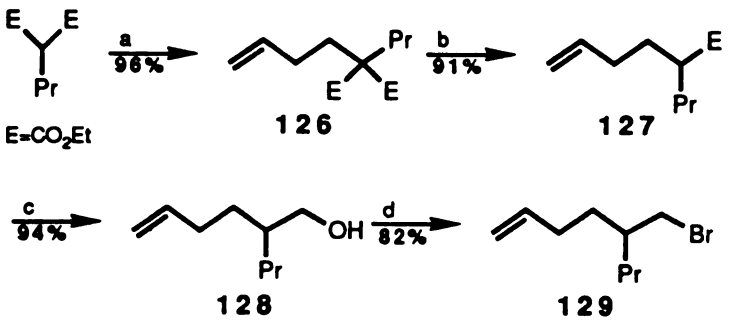


(a) LDA, THF, -78 °C; nBuLi, -78 °C; D_2O. (b) LAH, Et_2O; NaOH, H_2O. (c) NBS, PPh_3, CH_2Cl_2.

Compound **129**, to be used in a competitive rate experiment with **125**, was prepared in four linear steps beginning from the commercially available diethyl propylmalonate (Scheme 17). Enolate formation of the malonate derivative was accomplished with NaH in DMF and then subsequently coupled with 4-bromo-1-butene to provide **126** in 96% yield.[19] Deethoxycarboxylation was encouraged by the action of LiCl and H_2O in refluxing DMSO, which resulted in the formation of ester **127** (91% yield).[19] Conversion of **127** into **129** was brought about by adjustment of the oxidation state of **127** with LAH to

the alcohol level (**128**, 94% yield), followed by functional group manipulation to give bromide **129** (82% yield).

Scheme 17. Synthetic Route to 129

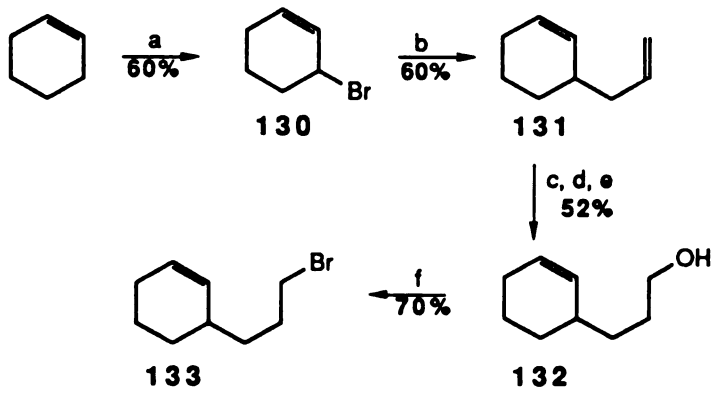


(a) NaH, DMF; 4-Bromo-1-butene. (b) LiCl, H_2O, DMSO, 185 °C. (c) LAH, Et_2O; NaOH, H_2O. (d) NBS, PPh_3, CH_2Cl_2.

An ongoing project in our group deals with the synthesis of multiple ring compounds. Cyclization of **133** (Scheme 18) would provide the bicyclo[4.3.0]nonane, which is common to many families of natural products. Synthesis of **133** required six linear steps beginning with radical bromination of cyclohexene, accomplished with NBS and peroxides (**130**; 60% yield).[53] Numerous literature methods for allylic coupling were attempted to prepare **131**.[54] After many sophisticated organometallic routes failed to give sufficeint quanities of **131**, recourse to a simple Grignard coupling was pursued. Thus, when allylmagnesium bromide[55] was reacted with **130**, the key carbon-carbon bond formation was secured (**131**; 60% yield). Next, a chemo- and regioselective oxidation of the terminal olefin was needed. Through the use of a bulky borane,[56] this turned out to be a trivial transformation. Addition of **131** to a THF solution of dicyclohexylborane, followed by oxidation with peroxides,[57] resulted in a single structural isomer (**132**). To facilitate the chromatographic separation of **132** from the reagent byproduct cyclohexanol, the 1° alcohol was selectively protected as the TBDMS ether.[58] Deprotection of the silyl ether with

TBAF, followed by chromatography, provided **132** in pure form (52% yield). Conversion of **132** to **133** was best accomplished by transforming the alcohol to the mesylate followed by displacement with LiBr. This sequence provided a modest yield of **133** (70% yield).[59]

Scheme 18. Synthetic Route to 133

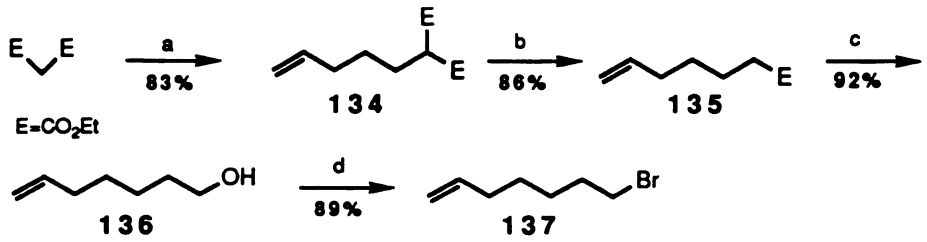


(a) NBS, CCl_4. (b) Allylmagnesium bromide, THF. (c) Dicyclohexylborohydride, THF; H_2O_2, NaOH. (d) TBDMSCl, DMAP, CH_2Cl_2; chromatographic separation. (e) TBAF; chromatographic separation. (f) MsCl, CH_2Cl_2; LiBr, THF.

3. Synthesis of Six-Membered Ring Precursor Substrates

The synthetic route for the parent substrate (**137**) is illustrated in Scheme 19. Alkylation of diethyl malonate with 5-bromo-1-pentene furnished **134** (83% yield), which was subsequently treated with LiCl and H_2O in refluxing DMSO to provide ester **135** (86% yield). Reduction of the ester followed by bromination of the resulting alcohol (**136**, 92% yield), completed the synthesis of bromide **137** (89% yield).

Scheme 19. Synthetic Route to 137

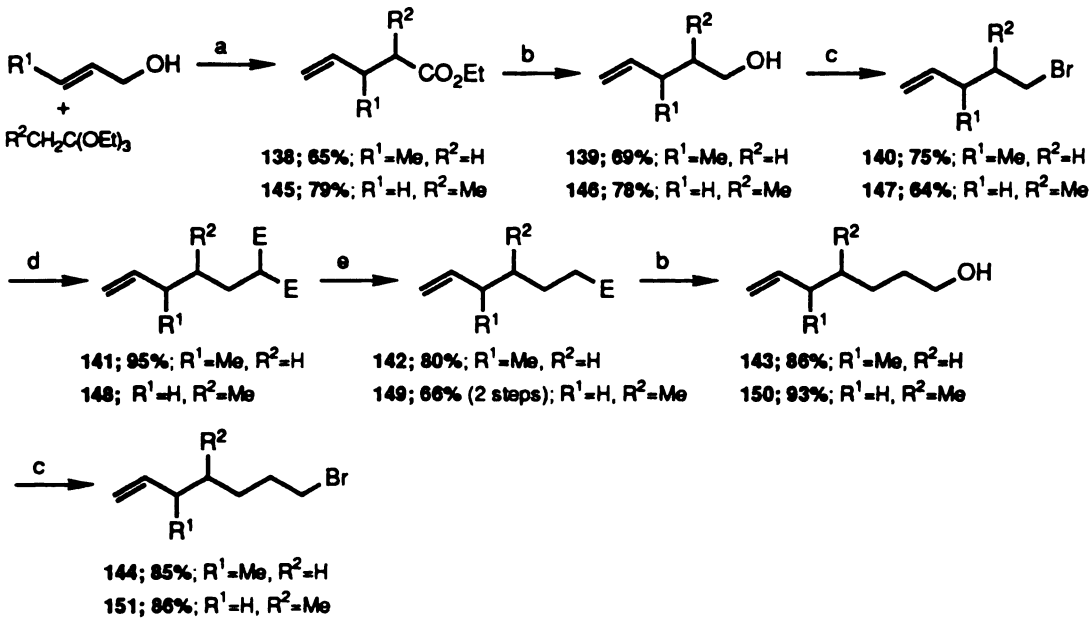


(a) NaH, DMF; 5-Bromo-1-pentene. (b) LiCl, H_2O, DMSO, 180 °C. (c) LAH, Et_2O; NaOH, H_2O. (d) NBS, PPh_3, CH_2Cl_2.

Scheme 20 illustrates the synthesis of the allylic- (**144**) and the homoallyic (**151**) methyl-7-bromo-1-heptenes. The key bromides **140** and **147**, needed for coupling with diethylmalonate, were prepared from esters **138** and **145**, which were accessible by employing the ortho-ester Claisen methodology. For example, crotyl alcohol was heated with triethyl orthoacetate and an acid catalyst to provide **138** in 65% yield.[60] Treatment of **138** with LAH (**139**, 69% yield) followed by bromination gave **140** (75% yield). In a similar fashion, allyl alcohol was condensed with triethyl orthopropionate and rearranged to ester **145** (79% yield), which was subsequently reduced (**146**, 78% yield) and brominated (**147**, 64% yield). Following the usual sequence of reactions, **140** and **147** were converted to the key cyclization substrates, **144** and **151**, in 56% and 53% overall yield.

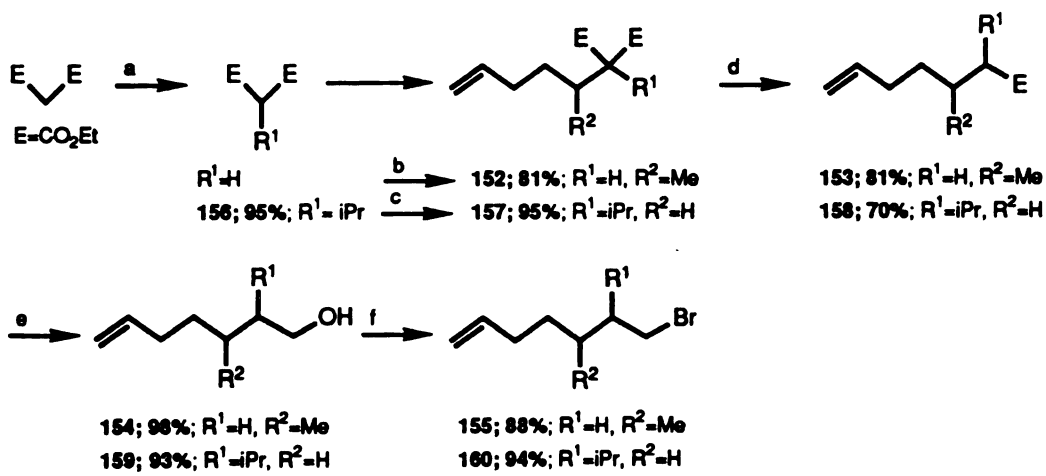
Moreover, Scheme 21 illustrates the synthesis of **155** and **160**, prepared in the usual fashion, which were synthesized in 57% and 55% overall yield, respectively.

Scheme 20. Synthetic Route to 144 and 151



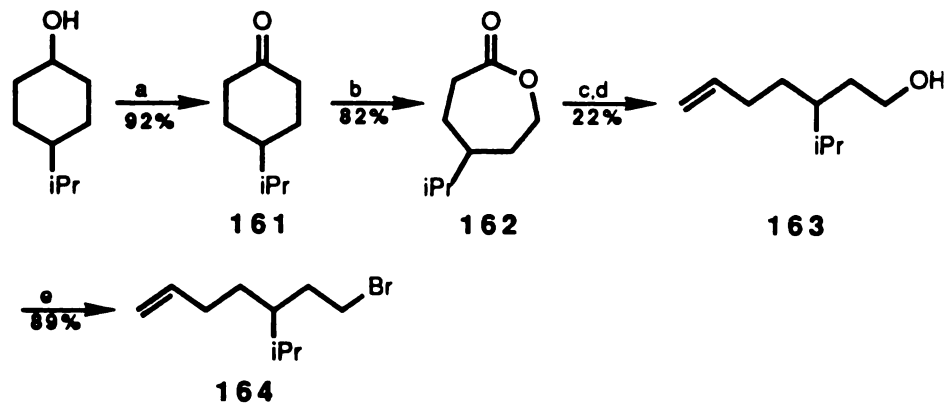
(a) $(H_3C)_3CO_2H$, 145 °C. (b) LAH, Et_2O; NaOH, H_2O. (c) NBS, PPh_3, CH_2Cl_2. (d) Diethyl malonate, NaH, DMF. (e) LiCl, H_2O, DMSO, 180 °C.

Scheme 21. Synthetic Route to 155 and 160



(a) NaH, DMF; 2-Bromopropane. (b) NaH, DMF; 5-Bromo-1-hexene. (c) NaH, DMF; 5-Bromo-1-pentene. (d) LiCl, H_2O, DMSO, 185 °C. (e) LAH, Et_2O; NaOH, H_2O. (f) NBS, PPh_3, CH_2Cl_2.

Scheme 22. Synthetic Route to 164



(a) Jones' reagent, Et_2O. (b) mCPBA, CH_2Cl_2. (c) DiBAl, toluene, -78 °C. (d) Ph_3PCH_2; H_3O^+. (e) NBS, PPh_3, CH_2Cl_2.

Jones' oxidation[61] of 4-isopropylcyclohexanol (Scheme 22) provided ketone **161** (92% yield), which was further oxidized using mCPBA[62] to give caprolactone **162** (82% yield). The reductive-olefination sequence, **162** to **163**, proved to be troublesome, however, after a number of attempts and chromatographic purification, **163** was in hand albeit in only 22% yield. Lactone **161** was reduced with DiBAl to the lactol at -78 °C, and olefinated with the methyl Wittig reagent, which secured the alkenol.[63] Conversion of **163** to bromide **164** was performed with NBS and PPh_3 without further difficulties (89% yield).

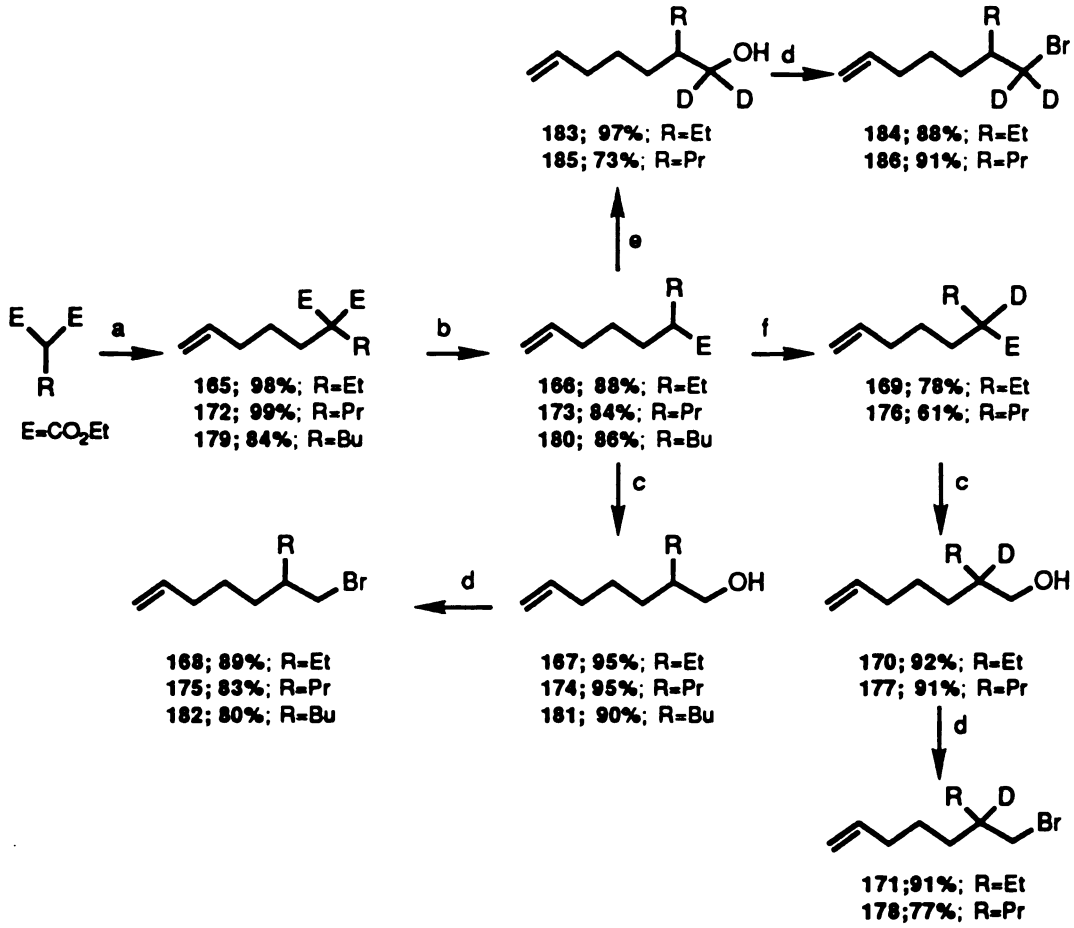
4. Synthesis of Competitive Rate Substrates

Our interest in the elucidation of the mechanism of Ziegler-Natta polymerization has compelled us to design an experiment to test whether α- and/or β-activation contribute to the mechanism. Substrates **168**, **171**, **175**, **178**, **182**, **184**, and **186** (Scheme 23) were chosen to test our hypothesis.[64] Upon examination of Scheme 23, three unique, yet similar, linear sequences

were envisioned in which three intermediates (**166**, **173**, and **180**) were common to all. Reaction of the enolate from the appropriate malonate (R= ethyl, propyl, or butyl) with 5-bromo-1-pentene in DMF provided **165**, **172**, and **179**, which were independently carried on to the respective esters. At this juncture, the three sequences diverged. The aforementioned esters were reduced and brominated to provide **168**, **175**, and **182**, respectively. The second sequence involved reduction of esters **166** and **173** with LAD followed by bromination, which furnished α,α-dideuterio bromides **184** and **186**. Finally, conversion of esters **166** and **173** to the β-deuterio esters **169** and **176** was accomplished, as previously described and carried on to bromides **171** and **178** in the usual fashion.

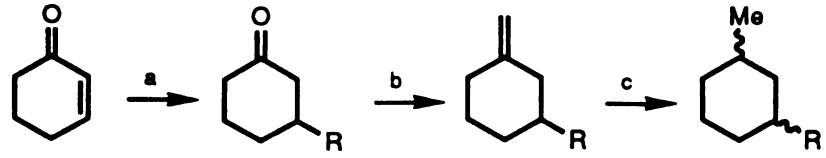
Schemes 24 and 25 illustrate the sequences performed to prepare the expected products of cyclization for the appropriate substrates. In Scheme 24, cyclohexenone was reacted at low temperatures with the appropriate Grignard reagent in the presence of a catalytic amount of a copper salt.[65,66] The resultant β-alkyl ketones were methylenated *via* Corey's procedure.[67] Finally, hydrogenation of the exocylic olefins provided a mixture of the *cis*- and *trans*-dialkylcyclohexanes.[68] In a similar manner, ketone **161** was methylenated and hydrogenated to provide **197**.

Scheme 23. Synthetic Route to Competitive Rate Substrates



(a) NaH, DMF; 5-Bromo-1-pentene. (b) LiCl, H_2O, DMSO, 180 °C. (c) LAH, Et_2O; NaOH, H_2O. (d) NBS, PPh_3, CH_2Cl_2. (e) LAD, Et_2O; NaOH, H_2O. (f) LDA, THF, -78 °C; nBuLi, -78 °C; D_2O.

Scheme 24. Synthetic Route to Cyclohexane Standards



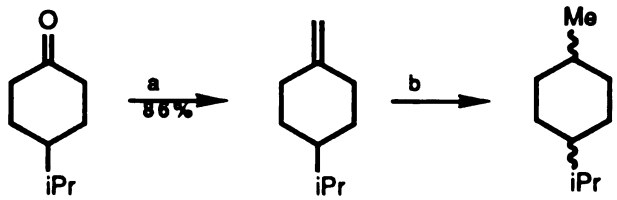
187; 82%; R=Et
190; 57%; R=Pr
193; 78%; R= iPr

188; 71%; R=Et
191; 71%; R=Pr
194; 89%; R= iPr

189; R=Et
192; R=Pr
195; R= iPr

(a) $CuIP(nBu)_3$, RMgBr, Et_2O; H_3O^+. (b) Ph_3PCH_2, DMSO. (c) H_2, PtO_2.

Scheme 25. Synthetic Route to 196 and 197



162 **196** **197**

(a) Ph_3PCH_2, DMSO. (b) H_2, PtO_2, MeOH.

5. Conclusion

The preparation of the substrates needed for the diastereoselective five-membered ring formation (Chapter 2), diastereoselective six-membered ring formation (Chapter 3), and our mechanistic studies (Chapter 4) was described. In all cases, recourse to established literature methods was utilized.

6. Experimental

General Methods. 6-Bromo-3-methyl-1-hexene (**36a**), 6-bromo-4-methyl-1-hexene (**36b**), 6-bromo-5-methyl-1-hexene (**36c**) and 6-bromo-6-methyl-1-hexene (**36d**) were kindly provided by Dr. J. R. Stille. Diethyl 2-butyl-2-(4-pentenyl)-propanedioate (**179**), 2-butyl-6-heptenoate (**180**), 2-butyl-6-hepten-1-ol (**181**), and 7-bromo-6-butyl-1-heptene (**182**) were kindly donated by Nancy S. Barta. 7-Bromo-6-methylhept-1-ene was provided by Steve Gabel. The following cyclization standards were purchased from either Aldrich Chemical Co. or Wiley Organics: *cis*- and *trans*-1,2- and 1,3-dimethylcyclopentane, methylcyclopentane, *cis*- and *trans*-1,2-, 1,3-, and 1,4-dimethylcyclohexane, cyclohexane, methylcyclohexane, cycloheptane, methylcycloheptane, and bicyclo [4.3.0] nonane. Me_2AlCl and $EtAlCl_2$ were purchased from Aldrich Chemical Co. from which stock solutions were prepared. Tetrahydrofuran (THF), diethyl ether (Et_2O), toluene, and benzene, when used as solvents, were distilled from sodium/benzophenone prior to use. Hexane was stirred over sulfuric acid for five days, then washed sequentially with water, saturated $NaHCO_3$, dried over $CaCl_2$, and the supernatant was distilled from sodium/benzophenone/tetraglyme. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 prior to use. Anhydrous dimethylsulfoxide and N,N-dimethylformamide were purchased from Aldrich. All reactions were conducted under nitrogen or argon atmospheres.

NMR spectra were obtained on a Varian Gemini 300 or a VXR-300 instrument with $CDCl_3$ as solvent. Signals are reported in units of ppm relative to the residual chloroform peak. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), oct (octet), m (multiplet), or b (broad). ^{13}C NMR resonances for carbons containing a carbon-

deuterium were not observed due to the quadrapolar effect caused by the deuterium atom. Infrared spectra (IR) were obtained on a Nicolet FT-IR 42 spectrometer using NaCl plates with thin films of organic compounds and reported in cm^{-1}. Analytical gas chromatography (GC) was performed on a Perkin Elmer 8500 instrument with a 50 m RSL200 column (5% methyl phenyl silicone equivalent to SE-54 or DB-5). All GC yields described were calculated by comparison to an internal standard and corrected for detector response.

Ethyl 2-methyl-2-deuterio-5-hexenoate (123). A solution of LDA was prepared by adding n-BuLi (2.29 M in hexanes, 10.1 mL, 23.1 mmol) to a 0 °C solution of DIPA (2.55 g, 25.2 mmol) in THF (30 mL). Stirring was continued for 30 minutes and the mixture was cooled to -78 °C. Ethyl 2-methyl-5-hexenoate (3.28 g, 21 mmol) was added dropwise to the LDA solution and stirred for 50 minutes. n-BuLi (2.29 M in hexanes, 13.80 mL, 31.5 mmol) was added to the reaction mixture at -78 °C (to deprotonate DIPA), stirred for 30 minutes, quenched with D_2O (10 mL), and warmed to ambient temperature. The aqueous layer was extracted with diethyl ether (4 x 20 mL). The combined diethyl extracts were concentrated and redissolved in diethyl ether (60 mL). The diethyl ether solution was washed with 1M HCl (2 x 30 mL), saturated $NaHCO_3$ (2 x 60 mL), saturated NaCl (60 mL), dried over $MgSO_4$, filtered, and conentrated to an oil. The crude residue was distilled under reduced pressure (bp_{22} 70-80 °C) and 2.10 g of **123** were obtained (64% yield). ^1H NMR (300 MHz) ($CDCl_3$) δ 1.11 (s, 3H), 1.22 (t, J = 7 Hz, 3H), 1.30-1.52 (m, 1H), 1.67-1.79 (m, 1H), 2.03 (tq, J = 1, 7 Hz, 2H), 4.10 (q, J = 7 Hz, 2H), 4.93 (ddt, J = 10, 2, 1 Hz, 1H), 4.98 (dq, J = 17, 2 Hz, 1H), 5.75 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.22, 16.88, 31.32, 32.74, 60.11, 114.96, 137.92, 176.00.

General Procedure For The Reduction Of Esters- 2-Deuterio-2-methyl-5-hexen-1-ol (124). A 100 mL flask, equipped with a dropping funnel, was loaded

with LAH (0.36 g, 9.36 mmol), suspended with diethyl ether (35 mL), and cooled to 0 °C. A solution of **123** (2.10 g, 13.38 mmol) in diethyl ether (40 mL) was added to the LAH suspension over 30 minutes. Stirring was continued at 0 °C for 1 hour, after which the dropping funnel was replaced with a reflux condenser and the reaction was heated to reflux for 3 hours. The reaction mixture was cooled to 0 °C and quenched by the slow sequential addition of H_2O (0.36 mL), 15% NaOH (0.36 mL), H_2O (1.08 mL) and stirred for 8 hours. The white precipitate was removed by filtration through a pad of silica gel on top of a glass frit. Concentration of the solution by rotary evaporation followed by distillation of the final residue (bp_{18} 70-80 °C) provided 1.40 g of **124** (91% yield); ^1H NMR (300 MHz) ($CDCl_3$) δ 0.88 (s, 3H), 1.08-1.22 (m, 1H), 1.40-1.58 (m, 1H), 1.74 (bs, 1H), 1.88-2.18 (m, 2H), 3.38 (d, J = 10 Hz, 1H), 3.46 (d, J = 10 Hz, 1H), 4.91 (dq, J = 10, 2 Hz, 1H), 4.97 (dq, J = 17, 2 Hz, 1H), 5.77 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 16.26, 31.09, 32.15, 67.99, 114.33, 138.87.

General Procedure For The Bromination Of Alcohols- 6-Bromo-5-deuterio-5-methyl-1-hexene (125). Triphenylphosphine (3.15 g, 12.0 mmol) and alcohol **124** (1.15 g, 10.0 mmol) were combined and diluted with CH_2Cl_2 (20 mL), and cooled to 0 °C. NBS (2.14 g, 12.0 mmol) was added over 2 hours by means of a solid addition funnel, stirred for 1 hour at 0 °C, and an additional 3 hours at ambient temperature. The reaction mixture was concentrated to a slurry by rotary evaporation, and the resulting solids were dissolved in a minimum of CH_2Cl_2. To this solution was added 50 mL petroleum ether (bp 30-65 °C) at ambient temperature, stirred for 10 minutes, and cooled to 0 °C for an additional 10 minutes. The supernatant was filtered *via* cannula, with a piece of filter paper attached to the end of the cannula, using a positive pressure of argon. The solids were washed sequentially with petroleum ether (2 x 25 mL) at 0 °C as before. This filtration sequence was performed twice more. The organic fractions were

combined and concentrated by rotary evaporation to approximately 15 mL and then filtered through a plug of basic alumina. The remaining solvent was removed by rotary evaporation and the residue was purified by distillation (bp_{40} 65-75 °C) to provide 1.51 g of bromide **125** (84% yield); IR (Film) 3079, 2965, 2930, 2260, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.00 (s, 3H), 1.30 (m, 1H), 1.50 (m, 1H), 1.95-2.15 (m, 2H), 3.31 (d, J = 10 Hz, 1H), 3.37 (d, J = 10 Hz, 1H), 4.95 (ddt, J = 10, 2, 1 Hz, 1H), 5.01 (dq, J = 17, 2 Hz, 1H), 5.77 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 18.50, 31.01, 33.81, 41.18, 114.79, 138.29.

General Procedure For Alkylation Of Malonate Derivatives- Diethyl 2-(3-butenyl)-2-(propyl)-propanedioate (126). To a suspension of NaH (1.83 g, 76.39 mmol) in DMF (70 mL) was added diethyl propylmalonate (14.45 g, 71.4 mmol) over 15 minutes by means of a pressure-equalized dropping funnel. After the addition was complete, the reaction was stirred for 2 hours. 4-Bromo-1-butene (10.79 g, 80.0 mmol) was added over 15 minutes, stirred for 30 minutes, and then heated to 65 °C (generally 12-24 hours). When the alkylation was complete, the reaction mixture was cooled to 0 °C, diluted with diethyl ether (80 mL), and quenched with H_2O (100 mL). The aqueous layer was extracted with diethyl ether (3 x 80 mL). The combined extracts were washed with H_2O (2 x 50 mL), saturated NaCl (60 mL), and dried over $MgSO_4$. The organic solution was filtered through silica on a glass frit, eluted with diethyl ether, and the solvent was evaporated. Distillation under reduced pressure ($bp_{<1}$ 70-80 °C) provided 17.58 g of **126** as a colorless oil (96% yield); IR (Film) 3081, 2967, 2876, 1732, 1644 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.07-1.20 (m, 2H), 1.20 (t, J = 7 Hz, 6H), 1.78-1.98 (m, 6H), 4.14 (q, J = 7 Hz, 4H), 4.88-5.03 (m, 2H), 5.65-5.82 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.04, 14.34, 17.34, 28.36, 31.53, 34.53, 57.27, 60.95, 114.83, 137.70, 171.68.

General Procedure For Deethoxycarboxylation of Malonate Derivatives- Ethyl 2-propyl-5-hexenoate (127). In a 250 mL flask were combined the following: **126** (17.0 g, 66.4 mmol), LiCl (5.35 g, 126.2 mmol), H_2O (1.20 g, 66.4 mmol), and DMSO (130 mL). The reaction mixture was heated to 185 °C until the malonate was consumed (generally 12-15 hours). After cooling to 0 °C, the reaction was diluted with H_2O (125 mL) and diethyl ether (85 mL). The aqueous phase was extracted with diethyl ether (5 x 75 mL) and the organic fractions were combined and washed with H_2O (75 mL), saturated $NaHCO_3$ (75 mL), and then saturated NaCl (75 mL). The organics were dried over $MgSO_4$, filtered through a pad of silica gel on top a glass frit, concentrated, and distilled under reduced pressure (bp_{15} 75-85 °C) which provided 11.10 g of **127** as a colorless oil (91% yield); IR (Film) 3079, 2961, 2938, 2874, 1736, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 3H), 1.25-1.76 (m, 6H), 1.95-2.06 (m, 2H), 2.33 (tt, J = 5, 9 Hz, 1H), 4.11 (q, J = 7 Hz, 2H), 4.84-5.02 (m, 2H), 5.75 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 13.96, 14.31, 20.53, 31.58, 34.60, 44.83, 59.99, 114.93, 137.98, 176.30. Two ^{13}C NMR resonances coincided in the spectrum.

2-Propyl-5-hexen-1-ol (128). Compound **127** (5.52 g, 30 mmol) was dissolved in diethyl ether (80 mL) and added dropwise to a 0 °C suspension of LAH (0.80 g, 21 mmol) in diethyl ether (70 mL). Following the usual workup, distillation of the crude residue (bp_{27} 85-95 °C) provided 4.01 g of **128** (94% yield); IR (Film) 3341, 3079, 2959, 2930, 2874, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.15-1.50 (m, 7H), 1.56 (bs, 1H), 2.05 (tq, J = 1, 7 Hz, 2H), 3.50 (m, 2H), 4.91 (ddt, J = 10, 2, 1 Hz, 1H), 4.98 (dq, J = 17, 2 Hz, 1H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.40, 19.91, 30.09, 31.06, 33.09, 39.66, 65.34, 114.32, 139.01.

6-Bromo-5-propyl-1-hexene (129). NBS (4.27 g, 24 mmol) was added slowly to a 0 °C solution of **128** (2.84 g, 20 mmol) and PPh_3 (6.29 g, 24 mmol) in CH_2Cl_2 (30 mL) according to the general procedure. After a typical workup and distillation, 3.35 g of bromide **129** (82% yield) were recovered (bp_{19} 75-80 °C); IR (Film) 3079, 2959, 2932, 2874, 2859, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.20-1.56 (m, 6H), 1.58-1.70 (m, 1H), 1.96-2.16 (m, 2H), 3.42 (dd, J = 5, 11 Hz, 1H), 3.46 (dd, J = 5, 11 Hz, 1H), 4.94 (ddt, J = 10, 2, 1 Hz, 1H), 5.01 (dq, J = 17, 2 Hz, 1H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.17, 19.65, 30.74, 31.67, 34.67, 38.44, 39.27, 114.75, 138.39.

3-Bromo-1-cyclohexene (130). A 1-L flask was loaded with NBS (39.14 g, 220 mmol), cyclohexene (16.4 g, 200 mmol), and a catalytic amount of benzoyl peroxide in CCl_4 (500 mL) and the mixture was brought to reflux for 4 hours. The reaction mixture was filtered, solvent evaporated, and the crude residue was distilled (bp_{40} 80 °C) to provide 18.13 g of **130** (60% yield); ^1H NMR (300 MHz) ($CDCl_3$) δ 1.60-2.30 (m, 6H), 4.70-4.90 (m, 1H), 5.75-5.83 (m, 1H), 5.85-5.93 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 18.47, 24.61, 32.65, 48.97, 128.84, 131.03.

3-(2-propenyl)-1-cyclohexene (131). Allylmagnesium bromide was prepared from allyl bromide (24.20 g, 200 mmol) and Mg (19.45 g, 800 mmol) in Et_2O (180 mL) as previously reported.[55] The resultant Grignard solution was determined to have a concentration of 1.07 M by titration with sec-butyl alcohol. The Grignard solution (100 mL, 107 mmol) was transferred to a 250 mL 3-necked flask equipped with a dropping funnel and a reflux condenser. A solution of **130** (7.00 g, 43.5 mmol) in THF (50 mL) was added dropwise to the Grignard solution over 60 minutes at ambient temperature and subsequently heated to reflux for 2-3 hours. After cooling to 0 °C, the solution was quenched with aqueous H_2SO_4 (20 mL H_2SO_4 in 50 mL H_2O). The aqueous layer was extracted with Et_2O (4 x 75 mL). The diethyl ether extracts were combined and washed with NaCl (2 x 100

mL), dried over Na_2SO_4, filtered through silica gel, and concentrated. The crude residue was distilled under reduced pressure (bp_{80} 70-80 °C) to provide 3.10 g of **131** (60% yield); IR (Film) 3077, 3019, 2928, 1668, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.14-1.28 (m, 1H), 1.42-1.58 (m, 1H), 1.64-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.00-2.07 (m, 2H), 2.05-2.20 (m, 1H), 4.95-5.05 (m, 2H), 5.52-5.70 (m, 1H), 5.62-5.60 (m, 1H), 5.77 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 21.41, 25.27, 28.79, 34.99, 40.64, 115.71, 127.20, 131.38, 137.25.

3-(3-Hydroxypropyl)-1-cyclohexene (132). Dicyclohexyl-borohyride (3.94 g, 22.1 mmol) was loaded into a 250 mL flask, equipped with a dropping funnel, under an atmosphere of nitrogen and diluted with THF (60 mL). Diene **131** (2.70 g, 22.1 mmol) was added dropwise to the solution, contained in a flask immersed in an ambient temperature water bath, and stirred for 5 hours during which time the diene was completely consumed. Oxidation of the trialkylborane was accomplished at 0 °C by the slow sequential addition of 3 M NaOH (7.4 mL) and 30% H_2O_2 (7.5 mL). The mixture was heated to 67 °C for 2 hours to facilitate complete oxidation. The solution was cooled to ambient temperature and saturated with K_2CO_3. The aqueous layer was extracted with diethyl ether (2 x 25 mL) and the organic fractions were combined and washed with H_2O (25 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. The crude residue contained the expected mixture of cylohexanol and **132**.

Separation of this mixture was found to be a difficult task; however, selective conversion of the 1° alcohol to the TBDMS ether allowed for trivial separation. To this end, the mixture of alcohols was dissolved in CH_2Cl_2 (75 mL) followed by the addition of DMAP (0.14 g, 1.10 mmol) and TEA (3.35 g, 33.15 mmol). Successive amounts of TBDMSCl were added until complete consumption of the 1° alcohol was achieved. The mixture was washed with H_2O (20 mL), NH_4Cl (20 mL), dried over $MgSO_4$, filtered, and concentrated to an oil.

The TBDMS ether was separated from cyclohexanol by washing the oil down a 6" silica gel column eluted with low-boiling petroleum ether (35-60°C). Removal of the solvent left behind an oil that contained the TBDMS ether of **132** and only a trace amount of the TBDMS ether of cyclohexanol; ^{13}C NMR (75 MHz) ($CDCl_3$) δ -5.25, 21.52, 25.37, 25.91, 25.98, 29.07, 30.26, 32.43, 34.96, 63.53, 126.83, 132.14.

Unmasking of the 1° alcohol was achieved by the addition of the silyl ethers to a 250 mL flask which contained TBAF (60 mL, 1M) in THF (60 mL) at 0 °C. The reaction mixture was diluted with diethyl ether (150 mL) and 1M HCl (60 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic fractions were washed with H_2O (25 mL), NaCl (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. Alcohol **132** was separated from the cyclohexyl-TBDMS ether by filtration of the oil down a 6" column of silica gel, eluted first with petroleum ether (which removed the TBDMS ether) and finally with diethyl ether (which removed the desired alcohol). After evaporation of the diethyl ether, the crude residue was distilled under reduced pressure (bp_{18} 100-115 °C) which provided 1.60 g of **132** (52% yield for 4 steps); IR (Film) 3339, 3017, 2934, 2859, 1670 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.10-1.88 (m, 9H), 1.90-1.96 (m, 2H), 1.98-2.10 (m, 1H), 3.61 (t, J = 7 Hz, 2H), 5.50-5.58 (m, 1H), 5.60-5.67 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 21.43, 25.31, 29.00, 30.11, 32.30, 34.90, 63.20, 127.05, 131.77.

3-(3-Bromopropyl)-1-cyclohexene (133). Conversion of **132** to the mesylate was achieved by the dropwise addition of methane sulfonyl chloride (1.26 g, 11 mmol) to a -10 °C solution of **132** (1.40 g, 10 mmol) and TEA (1.52 g, 11 mmol) in CH_2Cl_2 (50 mL). The mixture was allowed to stir for 45 minutes at -10 °C and 90 minutes at ambient temperature. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (20 mL), 10% HCl (30 mL), saturated

$NaHCO_3$ (30 mL), and saturated NaCl (30 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated to an oil. The mesylate was added to a -10 °C solution of LiBr (1.74 g, 20 mmol) in THF (30 mL). Stirring was continued for 30 minutes and the reaction was warmed to ambient temperatrure for 18 hours. After complete consumption of the mesylate, the mixture was filtered through basic alumina, eluted with diethyl ether, and concentrated to an oil. The oil was redissolved in diethyl ether (60 mL) and sequentially washed with saturated $NaHCO_3$ (20 mL), saturated NaCl (20 mL), dried over $MgSO_4$, filtered, and concentrated to an oil. The crude residue was distilled (bp_{10} 90-100°C) and 1.40 g of **133** were recovered (70% yield); IR (Film) 3017, 2930, 2856, 1672, 1449, 1437 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.14-1.26 (m, 1H), 1.29-1.60 (m, 3H), 1.64-1.82 (m, 2H), 1.82-2.00 (m, 4H), 1.98-2.14 (m, 1H), 3.38 (t, J = 7 Hz, 2H), 5.47-5.56 (m, 1H), 5.61-5.70 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 21.37, 25.26, 28.89, 30.29, 34.14, 34.48, 34.78, 127.37, 131.31.

Diethyl 2-(pent-4-enyl)-propanedioate (134). The following reagents were combined in the usual fashion: diethylmalonate (10.75 g, 67.2 mmol), NaH (1.69 g, 70.6 mmol) in DMF (60 mL), and 5-bromo-1-pentene (12.0 g, 80.6 mmol). Coupling was achieved by heating the mixture at 65 °C for 24 hours. After workup and distillation under reduced pressure (bp_3 112-115 °C), 12.71 g of **134** were recovered (83% yield): IR (Film) 2982, 2938, 1755, 1734, 1642, 1460, 1446 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 6H), 1.40 (tt, J = 8, 7 Hz, 2H), 1.88 (q, J = 8 Hz, 2H), 2.05 (q, J = 7 Hz, 2H), 3.29 (t, J = 8 Hz, 1H), 4.16 (q, J = 7 Hz, 4H), 4.90-5.15 (m, 2H), 5.75 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.05, 26.54, 28.17, 33.24, 51.91, 61.23, 114.95, 137.92, 169.42.

Ethyl-6-heptenoate (135). Compound **134** (8.75 g, 38.4 mmol) was combined with LiCl (3.09 g, 72.9 mmol) and H_2O (0.69 g, 38.4 mmol) in DMSO (80 mL) and heated to 185 °C for 18 hours. After the usual workup, 5.16 g of

ester **135** were obtained (86% yield) after distillation (bp_{22} 72-75 °C); IR (Film) 3079, 2980, 2936, 2865, 1738, 1642, 1462, 1446, 1420 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.39 (quint, J = 7 Hz, 2H), 1.61 (quint, J = 7 Hz, 2H), 2.03 (q, J = 7 Hz, 2H), 2.27 (t, J = 7 Hz, 2H), 4.09 (q, J = 7 Hz, 2H), 4.88-5.02 (m, 2H), 5.76 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.21, 24.40, 28.33, 33.32, 34.16, 60.13, 114.60, 138.39, 173.63.

6-Hepten-1-ol (136). Compound **135** (4.70 g, 30.1 mmol) was dissolved in diethyl ether (50 mL) and added dropwise to a suspension of LAH (0.80 g, 21.1 mmol) in diethyl ether (100 mL) as described in the general procedure. Following the usual workup, distillation of the crude residue (bp_{27} 75-85°C) provided 3.15 g of **136** (92% yield); IR (Film) 3337, 3079, 2998, 2978, 2936, 2861, 1642, 1462, 1437 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.25-1.43 (m, 4H), 1.53 (quint, J = 7 Hz, 2H), 1.86-1.96 (bs, 1H), 2.02 (q, J = 7 Hz, 2H), 3.58 (t, J = 6 Hz, 2H), 4.82-5.01 (m, 2H), 5.76 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 25.17, 28.62, 32.51, 33.64, 62.75, 114.29, 138.79.

7-Bromo-1-heptene (137). The following reagents were combined the according to the general procedure: alcohol **136** (1.50 g, 13.2 mmol), PPh_3 (4.14 g, 15.8 mmol), NBS (2.81 g, 15.8 mmol), and CH_2Cl_2.(20 mL). After distillation (bp_{44} 77-81 °C), 2.08 g of bromide **137** were recovered as a colorless oil (89% yield); IR (Film) 3077, 3000, 2977, 2961, 2938, 2859, 1642, 1460, 1439 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.32-1.52 (m, 4H), 1.78-1.90 (m, 2H), 1.98-2.10 (m, 2H), 3.38 (t, J = 7 Hz, 2H), 4.90-5.02 (m, 2H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 27.62, 28.01, 32.66, 33.50, 33.75, 114.57, 138.55.

Ethyl 3-Methyl-4-Pentenoate (138). In a 100 mL 3-necked flask equipped with a thermometer and a vigreux column with distillation head, were added crotyl alcohol (10 g, 139 mmol), triethyl orthoacetate (67.65 g, 417 mmol), and a catalytic amount of trimethyl acetic acid. This mixture was slowly heated to 145

°C which was maintained until a quanitative amount of ethanol was collected. After cooling the reaction to ambient temperature, H_2O (5.5 g, 306 mmol) was added and stirred for 4-6 hours. Heating was resumed to 110 °C until all of the ethanol and ethyl acetate had been collected, at which time the mixture was heated to distill the ester (**138**; bp_{760} 152-154 °C) which provided 11.71 g of **138** (63% yield); IR (Film) 2980, 2936, 2874, 1738, 1642, 1462, 1420 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.03 (d, *J* = 7 Hz, 3H), 1.22 (t, *J* = 7 Hz, 3H), 2.22 (dd, *J* = 15, 7 Hz, 1H), 2.32 (dd, *J* = 15, 7 Hz, 1H), 2.65 (m, 1H), 4.10 (q, *J* = 7 Hz, 2H), 4.93 (dt, *J* = 10, 2 Hz, 1H), 4.99 (dt, *J* = 17, 2 Hz, 1H), 5.74 (ddd, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.25, 19.68, 34.42, 41.34, 60.22, 113.27, 142.49, 172.55.

3-Methyl-4-penten-1-ol (139). A solution of **138** (11.0 g, 77.5 mmol, 220 mL Et_2O) was added to a suspension of LAH (2.06 g, 54.2 mmol) in Et_2O (170 mL). After the usual workup, **139** was distilled (bp_{760} 146-148 °C) and 5.35 g were collected (69% yield); IR (Film) 3339, 3081, 2963, 2932, 2876, 1640, 1454, 1420 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.00 (d, *J* = 7 Hz, 3H), 1.42-1.48 (bs, 1H), 1.50-1.60 (m, 2H), 2.28 (sept, *J* = 7 Hz, 1H), 3.63 (t, *J* = 7 Hz, 2H), 4.92 (dt, *J* = 10, 2 Hz, 1H), 4.98 (dt, *J* =17, 2 Hz, 1H), 5.69 (ddd, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 20.38, 34.89, 39.27, 61.21, 113.10, 144.23.

1-Bromo-3-methyl-4-pentene (140). The following reagents were combined according to the general procedure: **139** (5.15 g, 51.5 mmol), NBS (10.99 g, 61.8 mmol), PPh_3 (16.19 g, 61.8 mmol), and CH_2Cl_2 (65 mL). After distillation (bp_{75} 72-74 °C), 6.29 g of bromide **140** were recovered as a colorless oil (75% yield); IR (Film) 3079, 2969, 2930, 2869, 1642, 1455, 1435, 1418 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.01 (d, *J* = 7 Hz, 3H), 1.76-1.86 (m, 2H), 2.35 (sept, *J* = 7 Hz, 2H), 3.28-3.45 (m, 2H), 4.94-5.07 (m, 2H), 5.61 (ddd, *J* = 18, 10, 7

Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.91, 31.92, 36.54, 39.21, 114.15, 142.59.

Diethyl 2-(3-methyl-4-pentenyl)-propanedioate (141). Diethyl malonate (6.48 g, 40.5 mmol) was combined with NaH (1.01 g, 42.4 mmol) in DMF (32 mL) and subsequently reacted with **140** (5.70 g, 34.6 mmol) as described in the general procedure. After the usual workup, the residue was distilled under reduced pressure ($bp_{<1}$ 80-90 °C) which provided 8.02 g of **141** (95% yield); IR (Film) 3079, 2980, 2965, 2938, 2911, 1752, 1734, 1642, 1464 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.97 (d, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 6H), 1.19-1.35 (m, 2H), 1.75-1.95 (m, 2H), 2.00-2.20 (m, 1H), 3.26 (t, J = 7 Hz, 1H), 4.10-4.22 (m, 4H), 4.86-4.99 (m, 2H), 5.63 (ddd, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.05, 20.09, 26.52, 33.98, 37.57, 52.05, 61.25, 113.18, 143.76, 169.47, 169.50.

Ethyl 5-methyl-6-heptenoate (142). The following were combined and reacted according to the usual procedure: **141** (7.40 g, 30.6 mmol), LiCl (2.53 g, 59.7 mmol), H_2O (0.57 g, 31.4 mmol) and DMSO (65 mL). After workup and distillation (bp_{16} 80-85 °C), 4.12 g of ester **142** were recovered as a colorless oil (80% yield); IR (Film) 3079, 2963, 2934, 2911, 2872, 1740, 1642, 1456, 1420 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.96 (d, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.22-1.36 (m, 2H), 1.50-1.70 (m, 2H), 2.10 (sept, J = 7 Hz, 1H), 2.25 (t, J = 7 Hz, 2H), 4.09 (q, J = 7 Hz, 2H), 4.84-4.99 (m, 2H), 5.65 (ddd, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.23, 20.13, 22.70, 34.39, 35.96, 37.56, 60.18, 112.80, 144.26, 173.77.

5-Methyl-6-hepten-1-ol (143). Following the usual procedure, ester **142** (3.73 g, 21.9 mmol) was reduced with LAH (0.63 g, 16.5 mmol) in Et_2O (120 mL). After workup and distillation (bp_{30} 90-100 °C), 2.41 g of the alcohol were collected (86% yield); IR (Film) 3337, 3079, 2934, 2865, 1640, 1458, 1437, 1420 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.95 (d, J =7Hz, 3H), 1.15-1.40 (m, 4H), 1.40-1.60 (m,

2H), 1.5-1.8 (bs, 1H), 2.10 (sept, J = 7 Hz, 1H), 3.59 (t, J = 7 Hz, 2H), 4.82-4.98 (m, 2H), 5.65 (ddd, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 20.17, 23.38, 32.82, 36.35, 37.77, 62.95, 112.50, 144.66.

7-Bromo-3-methyl-1-heptene (144). According to the usual bromination procedure, alcohol **143** (2.0 g, 15.6 mmol), NBS (3.34 g, 18.8 mmol), and PPh_3 (4.91 g, 18.8 mmol) were combined and reacted in CH_2Cl_2 (20 mL). After a typical workup, 2.54 g of bromide **144** were recovered (85% yield) after distillation (bp_{14} 68-70 °C); IR (Film) 3079, 2963, 2936, 2865, 1642, 1456, 1439, 1431, 1420 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.97 (d, J = 7 Hz, 3H), 1.20-1.50 (m, 4H), 1.83 (quint, J = 7 Hz, 2H), 2.10 (sept, J = 7 Hz, 1H), 3.38 (t, J = 7 Hz, 2H), 4.90 (ddd, J = 10, 2, 1 Hz, 1H), 4.94 (ddd, J = 17, 2, 1 Hz, 1H), 5.66 (ddd, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 20.18, 25.84, 32.88, 33.89, 35.65, 37.64, 112.72, 144.39.

Ethyl 2-methyl-4-pentenoate (145). The ortho ester Claisen rearrangement was performed as described for **138**. Allyl alcohol (9.28 g, 160 mmol), triethyl orthopropionate (84.61 g, 480 mmol), and trimethyl acetic acid (1.64 g, 16 mmol) were combined and heated to 125 °C. After the reaction was quenched as in the usual fashion, 17.85 g of ester **145** were collected by distillation at atmospheric pressure (bp_{760} 154 °C, 79% yield); IR (Film) 3079, 2980, 2940, 2911, 1736, 1644, 1462 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.12 (d, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 2.08-2.22 (m, 1H), 2.32-2.54 (m, 2H), 4.10 (q, J = 7 Hz, 2H), 4.95-5.04 (m, 2H), 5.72 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.22, 16.51, 37.78, 39.21, 60.20, 116.73, 135.49, 176.10.

2-Methyl-4-penten-1-ol (146). Ester **145** (14.97 g, 105.4 mmol) was reduced with LAH (2.91 g, 76.7 mmol) in Et_2O (530 mL) by the usual procedure. After atmospheric distillation (bp 146 °C), 8.24 g of **145** was obtained as a colorless oil (78% yield); IR (Film) 3341, 3079, 2974, 2959, 2919, 2876, 1642,

1458, 1441, 1416 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.90 (d, J=7 Hz, 3H), 1.51 (bs, 1H), 1.71 (oct, J = 7 Hz, 1H), 1.86-1.98 (m, 1H), 2.09-2.20 (m, 1H), 3.43 (dd, J = 6, 11 Hz, 1H), 3.49 (dd, J = 6, 11 Hz, 1H), 4.85-5.05 (m, 2H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 16.34, 35.59, 37.80, 67.86, 116.04, 136.95.

5-Bromo-4-methyl-1-pentene (147). According to the usual bromination procedure, alcohol **146** (7.59 g, 75.9 mmol) was reacted with NBS (16.65 g, 93.6 mmol) and PPh_3 (24.52 g, 93.6 mmol) in CH_2Cl_2 (100 mL). Distillation of the crude residue at reduced pressure (bp_{70} 76-82 °C) furnished 7.85 g of **147** (64% yield); IR (Film) 3079, 2965, 2930, 2913, 2874, 1642, 1458, 1437 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 1.01 (d, J = 7 Hz, 3H), 1.87 (oct, J = 7 Hz, 1H), 1.96-2.07 (m, 1H), 2.13-2.25 (m, 1H), 3.31 (dd, J = 6, 10 Hz, 1H), 3.37 (dd, J = 6, 10 Hz, 1H), 5.00-5.10 (m, 2H), 5.72 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 18.54, 35.01, 39.06, 40.62, 116.98, 135.76.

Diethyl 2-(2-methyl-4-pentenyl)-propanedioate (148). The sodium enolate of diethyl malonate, prepared by reacting diethyl malonate (7.89 g, 49.3 mmol) and NaH (1.18 g, 49.3 mmol) in DMF (40 mL), was coupled with **147** (7.24 g, 44.8 mmol) in the usual manner. After workup and distillation ($bp_{<1}$ 80-90 °C), 9.40 g of diester **148** was isolated (87% yield). This compound was carried on without characterization.

Ethyl 4-methyl-6-heptenoate (149). By following the general procedure, **148** (9.40 g, 38.8 mmol) was deethoxycarboxylated by the combined action of LiCl (3.13 g, 73.8 mmol) and H_2O (0.73 g, 40.7 mmol) in DMSO (80 mL) at 185 °C. After the usual workup, the crude residue was distilled under reduced pressure (bp_{16} 80-85 °C) which provided 4.95 g as a colorless oil (66% yield for 2 steps); IR (Film) 3079, 2978, 2961, 2932, 2874, 1740, 1642, 1462, 1449 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 3H), 1.37-1.57 (m,

2H), 1.61-1.74 (m, 1H), 1.82-1.95 (m, 1H), 1.98-2.10 (m, 1H), 2.19-2.37 (m, 2H), 4.10 (q, J = 7 Hz, 2H), 4.95-5.05 (m, 2H), 5.74 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.20, 19.02, 31.38, 32.11, 32.33, 41.00, 60.20, 115.94, 136.97, 173.95.

4-Methyl-6-hepten-1-ol (150). A solution of ester **149** (4.40 g, 25.9 mmol) was added to a 0 °C suspension of LAH (0.69 g, 18.1 mmol) in diethyl ether (130 mL). The reaction mixture was purified in the usual manner which yielded 3.08 g (93 % yield) of **150** after distillation (bp_{30} 90-95 °C); IR (Film) 3335, 3077, 2955, 2934, 2872, 1642, 1458, 1441, 1416 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (d, J= 7 Hz, 3H), 1.04-1.22 (m, 1H), 1.28-1.64 (m, 4H), 1.73 (bs, 1H), 1.80-1.92 (m, 1H), 1.98-2.09 (m, 1H), 3.58 (t, J = 6 Hz, 2H), 4.92-5.00 (m, 2H), 5.74 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.36, 30.28, 32.38, 32.59, 41.31, 63.28, 115.65, 137.42.

7-Bromo-4-methyl-1-heptene (151). Alcohol **150** (1.46 g, 11.7 mmol), NBS (2.50 g, 14.1 mmol), and PPh_3 (3.68 g, 14.1 mmol) were combined in CH_2Cl_2 (15 mL) in the usual manner. After workup and distillation (bp_{14} 68-70 °C), 1.92 g of bromide **23** (86% yield) was obtained; IR (Film) 3079, 3002, 2961, 2913, 2874, 2855, 1642, 1460, 1439 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, J = 7 Hz, 3 H), 1.14-1.32 (m, 1H), 1.36-1.60 (m, 2H), 1.72-1.96 (m, 3H), 1.97-2.12 (m, 1H), 3.37 (t, J = 7 Hz, 2H), 4.93-5.03 (m, 2H), 5.66-5.83 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.34, 30.52, 32.20, 34.16, 34.95, 41.20, 115.89, 137.14.

Diethyl 2-(1-methyl-4-pentenyl)-propanedioate (152). The following reagents were combined as described in the general procedure: diethyl malonate (12.97 g, 81 mmol), NaH (1.97 g, 82.5 mmol), 5-bromo-1-hexene (12.00 g, 73.7 mmol) and DMF (50 mL). After a typical workup procedure, the crude residue was distilled ($bp_{<1}$ 80-90 °C) and 15.86 g of **152** was recovered (81% yield); IR (Film) 3079, 2982, 2938, 2878, 1736, 1642, 1466, 1449 cm^{-1}; ^1H NMR (300 MHz)

($CDCl_3$) δ 0.97 (d, J = 7 Hz, 3H), 1.18-1.35 (m, 1H), 1.24 (t, J = 7 Hz, 6H), 1.42-1.58 (m, 1H), 1.92-2.35 (m, 3H), 3.22 (d, J = 8 Hz, 1H), 4.17 (q, J = 7 Hz, 4H), 4.93 (ddt, J = 10, 2, 1 Hz, 1H), 4.99 (dq, J = 17, 2 Hz, 1H), 5.76 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.11, 16.76, 31.04, 32.81, 33.50, 57.66, 61.06, 61.12, 114.73, 138.21, 168.72, 168.86.

Ethyl 3-methyl-6-heptenoate (153). The following reagents were combined and heated to 185 °C for 15 hours: **152** (14.75 g, 62 mmol), LiCl (4.99 g, 117.8 mmol), H_2O (1.12 g, 62 mmol), and DMSO (115 mL). After the usual workup, distillation of the crude residue under reduced pressure (bp_{12} 86-90 °C) furnished 8.54 g of **153** (81% yield); IR (Film) 3079, 2979, 2932, 2876, 2853, 1738, 1642, 1460, 1418 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.92 (d, J = 6 Hz, 3H), 1.18-1.48 (m, 2H), 1.24 (t, J = 7 Hz, 3H), 1.88-2.14 (m, 4H), 2.27 (dd, J = 6, 14 Hz, 1H), 4.10 (q, J = 7 Hz, 2H), 4.86-5.04 (m, 2H), 5.77 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.26, 19.51, 29.86, 31.13, 35.82, 41.79, 60.07, 114.44, 138.60, 173.11.

3-Methyl-6-hepten-1-ol (154). Ester **153** (7.75 g, 46.5 mmol) was reduced with LAH (1.23 g, 32.5 mmol) in Et_2O (235 mL) following the general procedure. The alcohol was purified by distillation (bp_{25} 90-95 °C) and 5.74 g (98% yield) of **154** was obtained as a colorless oil; IR (Film) 3333, 3079, 2961, 2928, 2874, 1642, 1458 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, J = 7 Hz, 3H), 1.14-1.30 (m, 1H), 1.26-1.40 (m, 2H), 1.46-1.65 (m, 3H), 1.92-2.14 (m, 2H), 3.55-3.72 (m, 2H), 4.90 (ddt, J = 10, 2, 1 Hz, 1H), 4.97 (dq, J = 17, 2 Hz, 1H), 5.77 (ddt, J = 17, 10, 6 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.41, 29.00, 31.18, 36.23, 39.79, 61.02, 114.17, 139.03.

7-Bromo-5-methyl-1-heptene (155). According to the general procedure, NBS (5.00 g, 28.1 mmol) was combined with a solution of **154** (3.00 g, 23.4 mmol) and PPh_3 (7.37 g, 28.1 mmol) in CH_2Cl_2 (30 mL). The usual workup was

performed, and the crude residue was purified by distillation (bp_{17} 78-80 °C) which provided 5.74 g of bromide **155** (88% yield); IR (Film) 3079, 2965, 2930, 2872, 1642, 1458 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (d, *J* = 6 Hz, 3H), 1.22 (dddd, 1H), 1.41 (dddd, 1H), 1.56-1.72 (m, 2H), 1.78-1.94 (m, 1H), 1.94-2.15 (m, 2H), 3.33-3.48 (m, 2H), 4.93 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.78 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 18.76, 31.05, 31.18, 31.91, 35.64, 39.94, 114.42, 138.74.

Diethyl 2-(1-methylethyl)-propanedioate (156). The following reagents were combined and reacted as described in the general procedure; diethyl malonate (10.40 g, 65 mmol), NaH (1.71 g, 71.5 mmol), 2-bromopropane (10.30 g, 84.50 mmol) and DMF (55 mL). After workup and distillation ($bp_{<1}$ 50-55°C), 12.46 g of **156** was recovered (95% yield); IR (Film) 2971, 2942, 2909, 1736, 1468, 1448 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.94 (d, *J* = 7 Hz, 6H), 1.21 (t, *J* = 7 Hz, 6H), 2.25-2.42 (m, 1H), 3.05 (d, *J* = 9 Hz, 1H), 4.13 (q, *J* = 7 Hz, 4H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.03, 20.28, 28.64, 59.02, 60.99, 168.75.

Diethyl 2-(1-methylethyl)-2-(4-pentenyl)-propanedioate (157). The following reagents were combined and reacted as described in the general procedure; **156** (13.00 g, 64.40 mmol), NaH (1.69 g, 70.8 mmol), 5-bromopentene (11.99 g, 84.50 mmol) and DMF (60 mL). After workup and distillation ($bp_{<1}$ 80-85 °C), 16.22 g of **29** was recovered (93% yield); ^1H NMR (300 MHz) ($CDCl_3$) δ 0.94 (d, *J* = 7 Hz, 6 H), 1.23 (t, *J* = 7 Hz, 6H), 1.18-1.35 (m, 2H), 1.78-1.90 (m, 2H), 2.02 (tq, *J* = 1, 7 Hz, 2H), 2.29 (sept, *J* = 7 Hz, 1H), 4.16 (q, *J* = 7 Hz, 4 H), 4.92 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.97 (dq, *J* = 17, 2 Hz, 1H), 5.74 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.12, 18.55, 23.92, 31.87, 33.19, 33.97, 60.59, 61.57, 114.78, 138.19, 171.17.

Ethyl 2-(1-methylethyl)-6-heptenoate (158). Diester **157** (15.79 g, 58.5 mmol) was treated with LiCl (4.71 g, 111.2 mmol) and H_2O (1.05 g, 58.5 mmol) in

DMSO (120 mL) and heated to 185 °C for 15 hours. After a typical workup, the crude residue was distilled (bp_{20} 105-110 °C) and 8.08 g of ester **158** was recovered (70% yield); IR (Film) 2963, 2940, 2874, 1734, 1642, 1462, 1447 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, J = 7 Hz, 3H), 0.89 (d, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H), 1.25-1.39 (m, 2H), 1.40-1.64 (m, 2H), 1.81 (oct, J = 7 Hz, 1H), 1.95-2.10 (m, 3H), 4.10 (q, J = 7 Hz, 2H), 4.86-5.00 (m, 2H), 5.74 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.34, 20.19, 20.47, 26.98, 29.09, 30.63, 33.63, 52.63, 59.80, 114.54, 138.51, 175.80.

2-(1-Methylethyl)-6-hepten-1-ol (159). Ester **158** (7.66 g, 39.9 mmol) was reduced with LAH (1.06 g, 27.9 mmol) in Et_2O (200 mL) by the usual procedure. The alcohol was purified by distillation (bp_{10} 90-105 °C) and 5.62 g (93% yield) of **159** was obtained as a colorless oil; IR (Film) 3343, 3079, 2959, 2932, 2874, 1642, 1464, 1443, 1416 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (d, J = 7 Hz, 3H), 0.87 (d, J = 7 Hz, 3H), 1.15-1.50 (m, 6H), 1.70-1.88 (m, 1H), 1.96-2.07 (m, 2H), 3.44-3.60 (m, 2H), 4.85-5.05 (m, 2H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.18, 19.75, 27.13, 27.18, 27.83, 34.11, 46.46, 63.65, 114.35, 138.86.

7-Bromo-6-(1-methylethyl)-1-heptene (160). According to the general procedure, NBS (4.11g, 23.1 mmol) was combined with a solution of **159** (3.00 g, 19.2 mmol) and PPh_3 (6.05 g, 23.1 mmol) in CH_2Cl_2 (25 mL). The usual workup was performed and the crude residue was purified by distillation (bp_9 90-95 °C) which provided 3.94 g of bromide **160** (94% yield); IR (Film) 3079, 2963, 2934, 2872, 1642, 1462, 1441, 1416 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.88 (d, J = 7 Hz, 3H), 0.89 (d, J = 7 Hz, 3H), 1.25-1.50 (m, 5H), 1.79 (oct, J = 7 Hz, 1H), 1.95-2.10 (m, 2H), 3.44 (m, 2H), 4.94 (ddt, J = 10, 2, 1 Hz, 1H), 5.00 (dq, J = 17, 2 Hz, 1H), 5.79 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.17, 19.76, 26.65, 28.78, 29.19, 33.85, 37.41, 45.98, 114.57, 138.62.

4-(1-Methylethyl)-cylohexanone (161). To a solution of 4-(1-methylethyl)-cyclohexanol (12 g, 85.7 mmol) in diethyl ether (135 mL) was added 48 mL of a chromic acid solution. The two layers were separated, and the aqueous phase was extracted with diethyl ether (3 x 100 mL). The organic fractions were combined and washed with saturated $NaHCO_3$ (100 mL), saturated NaCl (100 mL), dried over $MgSO_4$, filtered through a pad of silica gel, eluted with diethyl ether, and the solvent was removed by rotary evaporation. Distillation at reduced pressure (bp_{20} 80-90 °C) provided 10.51 g of **161** (89% yield); IR (Film) 2961, 2932, 2872, 1721 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, J = 7 Hz, 6H), 1.30-1.60 (m, 4H), 1.90-2.02 (m, 2H), 2.19-2.40 (m, 4H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.89, 29.56, 31.69, 40.99, 42.44, 212.42.

4-(1-Methylethyl)-caprolactone (162). To an ambient temperature solution of ketone **33** (9.0 g, 64.3 mmol), $NaHCO_3$ (9.44 g, 112.5 mmol) in CH_2Cl_2 (425 mL) was added mCPBA (22.83 g, 112.5 mmol) over 2 hours, and the resultant solution was stirred for an additional 48 hours. After complete consumption of the ketone, the solution was washed with a 1N $NaHCO_3$ (270 mL), saturated NaCl (135 mL), and the solvent was removed by rotary evaporation. Lactone **34** was distilled under reduced pressure (bp_{20} 145-150 °C) using a Kugelrohr apparatus to provide 8.22 g of **162** (82% yield); IR (Film) 3019, 2963, 2934, 2874, 1734, 1719 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.84 (d, J = 7 Hz, 6H), 1.28-1.64 (m, 4H), 1.75-1.95 (m, 2H), 2.48-2.70 (m, 2H), 4.11 (dd, J = 9, 2 Hz, 1H), 4.21-4.32 (m, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.18, 19.29, 25.60, 31.93, 32.47, 33.31, 46.48, 68.42, 176.14.

3-(1-methylethyl)-6-hepten-1-ol (163). Methyltriphenylphosphonium bromide (10.31 g, 28.85 mmol) was loaded into a Schlenk flask, which was then evacuated, purged with argon, suspended in THF (135 mL), and cooled to -20 °C. nBuLi (11.15 mL, 2.5 M solution in hexane) was added to the Wittig salt, stirred for

1 hour, and cooled to -50 °C. In a separate flask, a solution of lactone **162** (3.0 g, 19.23 mmol) in toluene (100 mL) was cooled to -78 °C followed by the addition of a DiBAl solution (23.1 mL, 1.0 M in toluene) over 10 minutes and stirred for 1 hour. The lactol was warmed to 0 °C and transferred, *via* cannula, to the preformed ylide. The reaction temperature was maintained for 10 minutes at -50 °C, warmed to 0 °C for 30 minutes, and finally allowed to warm to ambient temperature. After 30 minutes at ambient temperature, an aqueous solution of $Na_2SO_4 \cdot H_2O$ (6.3 g) in H_2O (50 mL) was added to the reaction. The two layers were separated and the aqueous phase was extracted with diethyl ether (4 x 80 mL). The organic fractions were combined and washed with saturated NaCl (2 x 50 mL) dried over $MgSO_4$, and the organic solution was filtered through silica gel. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (silica gel 60 mesh, 8:2 diethyl ether:petroleum ether; R_f=0.51). The solvent was removed and the residue was distilled (bp_7 92-100° C) to give 650 mg **163** (22% yield); IR (Film) 3337, 3079, 2959, 2932, 2872, 1642, 1466 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.82 (d, J = 7 Hz, 3H), 0.83 (d, J = 7 Hz, 3H), 1.13-1.48 (m, 5H), 1.50-1.75 (m, 2H), 1.98-2.07 (m, 2H), 3.55-3.70 (m, 2H), 4.91 (ddt, J = 10, 2, 1 Hz, 1H), 4.98 (dq, J = 17, 2 Hz, 1H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 18.69, 19.15, 29.28, 30.03, 31.80, 33.61, 39.60, 61.81, 114.27, 139.14.

7-Bromo-5-(1-methylethyl)-1-heptene (164). Alcohol **163** (500 mg, 3.2 mmol), NBS (684 mg, 3.85 mmol), PPh_3 (1000 mg, 3.85 mmol), in CH_2Cl_2 (5 mL) were combined according to the general procedure. Following the usual workup, the crude residue was distilled (bp_{11} 88-92 °C) and 620 mg were collected (89% yield); IR (Film) 3079, 2961, 2932, 2872, 1642, 1466, 1439, 1416 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, J = 7 Hz, 6H), 1.14-1.44 (m, 4H), 1.54-1.92 (m, 4 H), 1.94-2.10 (m, 2 H), 3.39 (m, 2H), 4.94 (ddt, J = 10, 2, 1 Hz, 1H), 4.99 (dq, J = 17,

2 Hz, 1H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 18.77, 18.97, 28.80, 29.36, 31.62, 32.76, 34.07, 41.96, 114.50, 138.81.

Diethyl 2-(ethyl)-2-(4-pentenyl)-propanedioate (165). The following reagents were combined as outlined in the general procedure: diethyl ethylmalonate (37.64 g, 200 mmol), NaH (5.03 g, 210 mmol) in DMF (200 mL), and 5-bromo-1-pentene (32.16 g, 216 mmol). Coupling was achieved by heating the mixture at 50 °C for 40 hours. After workup and distillation under reduced pressure ($bp_{<1}$ 90-100°C), 50.08 g of **165** were recovered (98% yield); IR (Film) 2980, 2942, 2884, 1732, 1642 cm^{-1}; ^1H NMR (300 Mz) ($CDCl_3$) δ 0.78 (t, J = 7 Hz, 3H), 1.21 (t, J = 7 Hz, 6H), 1.14-1.28 (m, 2H), 1.76-1.95 (m, 4H), 2.03 (tq, J = 2, 7 Hz, 2H), 4.15 (q, J = 7 Hz, 4H), 4.88-5.01 (m, 2H), 5.75 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 8.39, 14.09, 23.24, 25.17, 31.06, 33.80, 57.82, 60.94, 114.89, 138.13, 171.82.

Ethyl 2-ethyl-6-heptenoate (166). Compound **165** (50.0 g, 195.3 mmol) was combined with LiCl (15.73 g, 371.1 mmol) and H_2O (3.51 g, 195.3 mmol) in DMSO (400 mL) and heated to 180 °C for 18 hours. After the usual workup, 31.61 g of ester **166** were obtained (88% yield) after distillation (bp_{10} 105-115 °C); IR (Film) 3079, 2967, 2934, 1734, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 3H), 1.27-1.68 (m, 6H), 2.02 (bq, J = 7 Hz, 2H), 2.23 (tt, J = 5, 9 Hz, 1H), 4.11 (q, J = 7 Hz, 2H), 4.87-5.02 (m, 2H), 5.75 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.80, 14.34, 25.48, 26.65, 31.49, 33.61, 47.18, 59.97, 114.58, 138.50, 176.29.

2-Ethyl-6-hepten-1-ol (167). Compound **166** (10.12 g, 55 mmol) was dissolved in diethyl ether (150 mL) and added dropwise to a 0 °C suspension of LAH (1.46 g, 38.5 mmol) in diethyl ether (125 mL). Following the usual workup, distillation of the crude residue (bp_{22} 90-100 °C) provided 7.39 g of **167** (95% yield); IR (Film) 3337, 3079, 2963, 2876, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$)

δ 0.87 (t, *J* = 7 Hz, 3H), 1.15-1.45 (m, 8H), 2.02 (bq, *J* = 7 Hz, 2H), 3.51 (m, 2H), 4.88-5.02 (m, 2H), 5.78 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.06, 23.28, 26.16, 29.88, 34.10, 41.86, 65.17, 114.36, 138.90.

7-Bromo-6-ethyl-1-heptene (168). NBS (4.27 g, 24 mmol) was added slowly to a 0 °C solution of **167** (2.84 g, 20 mmol) and PPh_3 (6.29 g, 24 mmol) in CH_2Cl_2 (25 mL). After a typical workup, 3.66 g of bromide **168** (89% yield) were recovered after distillation (bp_{24} 90-100 °C); IR (Film) 3079, 2965, 2934, 2876, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3H), 1.28-1.46 (m, 6H), 1.48-1.60 (m, 1H), 1.98-2.10 (m, 2H), 3.42 (dd, *J* = 5, 10-11 Hz, 1H), 3.44 (dd, *J* = 5, 10-11 Hz, 1H), 4.94 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.79 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 10.85, 25.12, 25.88, 31.65, 33.81, 38.93, 40.95, 114.55, 138.64.

Ethyl 2-deuterio-2-ethyl-6-heptenoate (169). According to the procedure described for **123**, ester **166** (6.44 g, 35 mmol) was added dropwise to a -78 °C THF (70 mL) solution of LDA (38.5 mmol) and stirred for 50 minutes. The reaction mixture was diluted with THF (20 mL) and n-BuLi (18.35 mL, 45.5 mmol) was added, stirred for 30 minutes, and quenched with D_2O (10 mL). After the usual workup, the crude residue was distilled under reduced pressure (bp_{21} 90-100°C) and 4.91 g of **169** were recovered (78% yield); IR (Film) 3079, 2977, 2936, 1734, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.86 (t, *J* = 7 Hz, 3H), 1.23 (t, *J* = 7 Hz, 3H), 1.26-1.68 (m, 6H), 2.01 (q, *J* = 7 Hz, 2H), 4.11 (q, *J* = 7 Hz, 2H), 4.92 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.96 (dq, *J* = 17, 2 Hz, 1H), 5.75 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.76, 14.33, 25.39, 26.62, 31.40, 33.60, 59.94, 114.57, 138.49, 176.29.

2-Deuterio-2-ethyl-6-hepten-1-ol (170). Ester **169** (4.47 g, 24.2 mmol) was dissolved in diethyl ether (75 mL) and added slowly to a 0 °C suspension of LAH (0.65 g, 17.0 mmol) in diethyl ether (50 mL) according to the general

procedure. Following the usual workup, distillation of the crude residue (bp_{22} 90-100 °C) provided 3.17 g of **170** (92% yield); IR (Film) 3343, 3079, 2963, 2861, 2130, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.18-1.42 (m, 7H), 2.03 (bq, J = 7 Hz, 2H), 3.52 (m, 2H), 4.94-5.02 (m, 2H), 5.79 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.05, 23.17, 26.14, 29.77, 34.12, 65.15, 114.39, 138.92.

7-Bromo-6-deuterio-6-ethyl-1-heptene (171). NBS (3.43 g, 19.3 mmol) was added slowly to a 0 °C solution of **170** (2.28 g, 16 mmol) and PPh_3 (5.05 g, 19.3 mmol) in CH_2Cl_2 (25 mL) according to the general procedure. After a typical workup, 2.99 g of bromide **171** (91% yield) were recovered after distillation (bp_{19} 80-90 °C); IR (Film) 3079, 2965, 2934, 2876, 2114, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.30-1.48 (m, 6H), 1.95-2.10 (m, 2H), 3.40 (d, J = 11 Hz, 1H), 3.44 (d, J = 11 Hz, 1H), 4.94 (ddt, J = 10, 2, 1 Hz, 1H), 4.99 (dq, J = 17, 2 Hz, 1H), 5.79 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 10.80, 25.00, 25.85, 31.53, 33.82, 38.82, 114.55, 138.65.

Diethyl 2-(4-pentenyl)-2-(propyl)-propanedioate (172). The following reagents were combined as described in the general procedure: diethyl propylmalonate (40.45 g, 200 mmol), NaH (5.03 g, 210 mmol) in DMF (200 mL), and 5-bromo-1-pentene (32.16 g, 216 mmol). Coupling was achieved by heating the mixture at 50 °C for 40 hours. After workup and distillation under reduced pressure ($bp_{<1}$ 95-110 °C), 53.6 g of **172** were recovered (99 % yield); IR (Film) 3079, 2965, 2876, 1734, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.07-1.27 (m, 4H), 1.21 (t, J = 7 Hz, 6H), 1.77-1.89 (m, 4H), 2.02 (bq, J = 7 Hz, 2H), 4.14 (q, J = 7 Hz, 4H), 4.89-5.02 (m, 2H), 5.74 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.09, 14.40, 17.36, 23.33, 31.71, 33.81, 34.46, 57.46, 60.94, 114.88, 138.14, 171.89.

Ethyl 2-propyl-6-heptenoate (173). Compound **172** (53.0 g, 196.3 mmol) was combined with LiCl (15.81 g, 373 mmol) and H_2O (3.53 g, 196.3 mmol) in DMSO (400 mL) and heated to 180 °C for 18 hours. After the usual workup, 32.49 g of ester **173** were obtained (84% yield) after distillation ($bp_{<1}$ 60-70 °C); IR (Film) 3079, 2959, 2938, 1734, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.19-1.66 (m, 8H), 1.23 (t, J = 7 Hz, 3H), 2.02 (bq, J = 7 Hz, 2H), 2.31 (tt, J = 5, 9 Hz, 1H), 4.11 (q, J = 7 Hz, 2H), 4.88-5.02 (m, 2H), 5.76 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.00, 14.33, 20.60, 26.66, 31.90, 33.60, 34.67, 45.36, 59.98, 114.58, 138.51, 176.47.

2-Propyl-6-hepten-1-ol (174). Compound **173** (10.89 g, 55 mmol) was dissolved in diethyl ether (150 mL) and added dropwise to a 0 °C suspension of LAH (1.46 g, 38.5 mmol) in diethyl ether (125 mL) as described in the general procedure. Following the usual workup, distillation of the crude residue (bp_{20} 90-100 °C) provided 8.16 g of **174** (95% yield); IR (Film) 3337, 3079, 2930, 2870, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.12-1.52 (m, 9H), 1.53 (bs, 1H), 1.94-2.06 (m, 2H), 3.44-3.54 (m, 2H), 4.86-5.02 (m, 2H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.40, 19.96, 26.14, 30.36, 33.16, 34.10, 40.14, 65.53, 114.34, 138.89.

7-Bromo-6-propyl-1-heptene (175). NBS (4.27 g, 24 mmol) was added slowly to a 0 °C solution of **174** (3.12 g, 20 mmol) and PPh_3 (6.29 g, 24 mmol) in CH_2Cl_2 (25 mL) according to the general procedure. After the typical workup, 3.63 g of bromide **175** (83% yield) were recovered after distillation (bp_{21} 100-110 °C); IR (Film) 3079, 2959, 2860, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.18-1.50 (m, 8H), 1.50-1.66 (m, 1H), 1.95-2.10 (m, 2H), 3.43 (d, J = 5 Hz, 2H), 4.93 (ddt, J = 10, 2, 1 Hz, 1H), 4.99 (dq, J = 17, 2 Hz, 1H), 5.79 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.17, 19.69, 25.83, 32.00, 33.82, 34.79, 39.13, 39.45, 114.54, 138.65.

Ethyl 2-deuterio-2-propyl-6-heptenoate (176). According to the procedure described for **123**, ester **173** (6.88 g, 35 mmol) was added dropwise to a -78 °C THF (70 mL) solution of LDA (38.5 mmol) and stirred for 50 minutes. The reaction mixture was diluted with THF (20 mL), n-BuLi (18.35 mL, 45.5 mmol) was added, stirred for 30 minutes, and quenched with D_2O (10 mL). After a typical workup, the crude residue was distilled under reduced pressure (bp_{21} 95-105 °C) which provided 4.19 g of **176** (61% yield); IR (Film) 3079, 2961, 2934, 2874, 2170, 1736, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.18-1.48 (m, 8H), 1.23 (t, J = 7 Hz, 3H), 1.50-1.64 (m, 2H), 2.02 (bq, J = 7 Hz, 2H), 4.11 (q, J = 7 Hz, 2H), 4.87-5.02 (m, 2H), 5.75 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 13.98, 14.33, 20.56, 26.63, 31.80, 33.59, 34.57, 59.95, 114.57, 138.49, 176.46.

2-Deuterio-2-propyl-6-hepten-1-ol (177). Compound **176** (3.87 g, 19.6 mmol) was dissolved in diethyl ether (60 mL) and added dropwise to a 0 °C suspension of LAH (0.52 g, 13.72 mmol) in diethyl ether (40 mL) as described in the general procedure. Following the usual workup, distillation of the crude residue (bp_{20} 90-100 °C) provided 2.78 g of **177** (91% yield); IR (Film) 3335, 3079, 2959, 2128, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.15-1.44 (m, 9H), 2.02 (tq, J = 2, 7 Hz, 2H), 3.50 (s, 2H), 4.91 (ddt, J = 10, 2, 1 Hz, 1H), 4.97 (dq, J = 17, 2 Hz, 1H), 5.78 (ddt, 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.43, 19.94, 26.11, 30.24, 33.05, 34.12, 65.51, 114.36, 138.91.

7-Bromo-6-deuterio-6-propyl-1-heptene (178). NBS (3.43 g, 19.3 mmol) was slowly added to a 0 °C solution of **177** (2.28 g, 14.5 mmol) and PPh_3 (5.06 g, 19.3 mmol) in CH_2Cl_2 (25 mL) according to the usual procedure. After a typical workup, 3.63 g of bromide **178** (77% yield) were recovered after distillation (bp_{21} 95-105 °C); IR (Film) 3079, 2961, 2932, 2128, 1642 cm^{-1}; ^1H NMR (300 MHz)

($CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3H), 1.20-1.45 (m, 8H), 1.98-2.08 (m, 2H), 3.42 (s, 2H), 4.94 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.79 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ14.18, 19.65, 25.79, 31.88, 33.82, 34.68, 39.33, 114.54, 138.65.

1,1-Dideuterio-2-ethyl-6-hepten-1-ol (183). Compound **166** (2.76 g, 15.0 mmol) was dissolved in diethyl ether (25 mL) and added dropwise to a 0 °C suspension of LAD (0.44 g, 10.5 mmol) in diethyl ether (50 mL) as described in the general procedure. Following the usual workup, distillation of the crude residue (bp_{20} 95-105 °C) provided 2.09 g of **183** (97% yield); IR (Film) 3345, 3079, 2965, 2934, 2863, 2197, 2093, 1642 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3H), 1.20-1.50 (m, 8H), 2.03 (tq, *J* = 1, 7 Hz, 2H), 4.92 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.98 (dq, *J* = 17, 2 Hz, 1H), 5.79 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.07, 23.24, 26.16, 29.84, 34.11, 41.66, 114.37, 138.91.

7-Bromo-7,7-dideuterio-6-ethyl-1-heptene (184). NBS (2.22 g, 12.5 mmol) was slowly added to a 0 °C solution of **183** (1.50 g, 10.4 mmol) and PPh_3 (3.28 g, 12.5 mmol) in CH_2Cl_2 (15 mL) according to the usual procedure. After a typical workup, 1.86 g of bromide **184** (88% yield) were recovered after distillation (bp_{19} 80-90 °C); IR (Film) cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3H), 1.28-1.46 (m, 6H), 1.46-1.58 (m, 1H), 1.98-2.10 (m, 2H), 4.94 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.79 (ddt, *J* = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 10.86, 25.07, 25.88, 31.60, 33.82, 40.71, 114.56, 138.65.

1,1-Dideuterio-2-propyl-6-hepten-1-ol (185). Compound **173** (2.97 g, 15.0 mmol) was dissolved in diethyl ether (25 mL) and added dropwise to a 0 °C suspension of LAD (0.44 g, 10.5 mmol) in diethyl ether (50 mL) as described in the general procedure. Following the usual workup, distillation of the crude residue (bp_{22} 105-115 °C) provided 1.72 g of **185** (73% yield); IR (Film) 3339,

3079, 2959, 2930, 2872, 2197, 2093, 1642, 1460, 1416 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3H), 1.17-1.49 (m, 10H), 2.02 (bq, J = 7 Hz, 2H), 4.87-5.02 (m, 2H), 5.78 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 14.39, 19.94, 26.10, 30.27, 33.08, 34.08, 39.92, 114.32, 138.88.

7-Bromo-6-deuterio-6-propyl-1-heptene (186). NBS (1.92 g, 10.8 mmol) was slowly added to a 0 °C solution of **185** (1.42 g, 9.0 mmol) and PPh_3 (2.83 g, 10.8 mmol) in CH_2Cl_2 (15 mL) according to the usual procedure. After a typical workup, 1.82 g of bromide **186** (91% yield) were recovered after distillation (bp_{22} 100-110 °C); IR (Film) 3079, 2959, 2930, 2872, 2861, 1642, 1458, 1416 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.18-1.50 (m, 8H), 1.52-1.65 (m, 1H), 1.97-2.01 (m, 2H), 4.90-5.04 (m, 2H), 5.79 (ddt, J = 17, 10, 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.19, 19.70, 25.83, 31.95, 33.83, 34.74, 38.90, 114.55, 138.66.

3-Ethylcyclohexanone (187). In a 100 mL Schlenk flask, equipped with a dropping funnel, were loaded magnesium turnings (7.78 g, 320 mmol), THF (60 mL), and a small crystal of iodine, and the flask was heated to 45 °C. Ethyl bromide (8.71 g, 80 mmol) was added dropwise over 2 hours and stirred an additional 4 hours. A separate 250 mL flask was loaded with n-Bu_3PCuI (1.99 g, 5.08 mmol), diluted with THF (10 mL), and cooled to -45 °C. The Grignard solution was transferred *via* cannula to the copper salt over 5 minutes and stirred for an additional 20 minutes. Cyclohexenone (3.70 g, x mmol) was added dropwise over 15 minutes, stirred for 90 minutes, and the solution was allowed to warm to -20 °C until all cyclohexenone was consumed. The reaction mixture was quenched with saturated NH_4Cl (8 mL) and diluted with petroleum ether (500 mL) The organic layer was washed with NH_4OH (3 x 100 mL; 6 mL NH_4OH in 294 mL H_2O), NaCl (40 mL), dried over $MgSO_4$, filtered through silica gel, concentrated to an oil, and distilled (bp_{20} 80-100 °C) which provided 3.96 g of **37** (82% yield); IR (Film) 2963, 2934, 2876, 1715 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (t, J = 7

Hz, 3H), 1.18-1.42 (m, 3H), 1.48-1.70 (m, 2H), 1.78-2.05 (m, 3H), 2.15-2.42 (m, 3H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ11.10, 25.22, 29.23, 30.82, 40.70, 41.43, 47.78, 212.07.

3-Ethylmethylenecyclohexane (188). NaH (0.39 g, 16.5 mmol) was loaded into a 250 mL flask under an atmosphere of nitrogen and suspended in DMSO (45 mL). The suspension was heated to 75 °C for 45 minutes or until no further H_2 was evolved. A separate flask was loaded methyltriphenylphosphonium bromide (5.90 g, 16.5 mmol), diluted with DMSO (30 mL), and heated to 50 °C until the solution was homogeneous. The Wittig salt was added to the dimsyl anion at ambient temperature and stirred for 30 minutes, during which time the solution became orange-red. Ketone **187** was added at room temperature and the heated to 55 °C. After the ketone was consumed, the reaction mixture was quenched with H_2O (25 mL) and extracted with petroleum ether (4 x 60 mL). The organic layers were combined and washed with (1:1) DMSO:H_2O (65 mL), NaCl (130 mL), dried over $MgSO_4$, filtered through neutral alumina, and concentrated. The crude residue was distilled (bp_{51} 60-65 °C) which provided 1.14 g of **188** was recovered (71% yield); IR (Film) 3073, 2963, 2932, 2876, 2859, 1651 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3H), 0.90-1.10 (m, 1H), 1.18-1.38 (m, 4H), 1.58-1.82 (m, 3H), 1.84-2.00 (m, 1H), 2.18-2.36 (m, 2H), 4.58 (bs, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.42, 27.13, 29.45, 32.21, 35.21, 40.95, 41.41, 106.66, 149.73.

1-Ethyl-3-methylcyclohexane (189). In 50 mL flask were loaded PtO_2 (25 mg), **188** (0.75 g, 6 mmol), and methanol (15 mL). The flask was filled and purged with H_2 three times and stirred under an atmosphere of H_2. The consumption of the olefin was monitored by NMR. GC analysis determined the ratio of isomers to be 1.96:1 (trans:cis); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 11.43,

11.97, 20.76, 20.87, 23.00, 26.37, 27.23, 27.28, 31.20, 31.30, 32.58, 32.73, 33.89, 34.23, 35.44, 38.93, 39.50, 41.99.

3-Propylcyclohexanone (190). The following reagents were combined according to the procedure described for **187**: propyl bromide (9.83 g, 80 mmol), Mg (7.78 g, 320 mmol) and THF (60 mL); n-Bu_3PCuI (1.99 g, 5.08 mmol) in THF (10 mL), and cyclohexenone (3.75 g, 39.1 mmol). The crude residue was distilled ($bp_{<1}$ 50-60 °C) and 3.13 g **190** was obtained (57% yield); IR (Film) 2959, 2872, 1713 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (t, J = 7 Hz, 3H), 1.16-1.38 (m, 5H), 1.50-1.90 (m, 3H), 1.92-2.06 (m, 2H), 2.14-2.42 (m, 3H); ^{13}C NMR (75 MHz) $CDCl_3$) δ 14.04, 19.67, 25.25, 31.23, 38.75, 38.77, 41.45, 48.12, 212.09.

3-Propylmethylenecyclohexane (191). The following reagents were combined as described for **188**; NaH (0.39 g, 16.5 mmol) in DMSO (45 mL); methyltriphenylphosphonium bromide (5.90 g, 16.5 mmol) in DMSO (30 mL), and **190** (1.93 g, 13.8 mmol). After workup and distillation (bp_{51} 70-80 °C), 1.32 g **191** was recovered (71% yield); IR (Film) 3071, 2980, 1651 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.86 (t, J = 7 Hz, 3H), 0.95-1.12 (m, 1H), 1.10-1.42 (m, 6H), 1.50-1.82 (m, 3H), 1.85-2.02 (m, 1H), 2.18-2.35 (m, 2H), 4.60 (bs, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$)δ 14.33, 19.93, 27.16, 32.59, 35.21, 38.89, 39.12, 41.79, 106.65, 149.76.

1-Methyl-3-propylcyclohexane (192). In a 25 mL flask were loaded PtO_2 (25 mg), **191** (0.82 g, 6 mmol), and diethyl ether (15 mL). The hydrogenation was carried out as in **189**. GC analysis determined the ratio of isomers to be 1.71:1 (trans:cis); ^{13}C NMR (75 MHz) ($CDCl_3$)δ 14.33, 15.22, 19.89, 20.46, 20.75, 20.88, 22.95, 26.38, 27.22, 31.64, 32.05, 32.72, 32.98, 33.89, 35.42, 36.92, 37.40, 39.25, 39.97, 42.40.

3-(1-methylethyl)-cyclohexanone (193). The following reagents were combined according to the procedure described for **187**: 2-bromopropane (7.37 g, 60 mmol), Mg (5.83 g, 240 mmol) in THF (60 mL); n-Bu_3PCuI (1.99 g, 5.08

mmol) in THF (10 mL); and cyclohexenone (3.53 g, 36.8 mmol). The crude residue was distilled (bp_{10} 80 °C) and 4.00 g **193** was obtained (78% yield); IR (Film) 2961, 2872, 1715, 1466, 1449, 1426 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (d, J = 6 Hz, 3H), 0.86 (d, J = 6 Hz, 3H), 1.25-1.40 (m, 1H), 1.45-1.62 (m, 3H), 1.78-1.85 (m, 1H), 1.95-2.10 (m, 2H), 2.15-2.38 (m, 3H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.25, 19.48, 25.47, 28.27, 32.42, 41.43, 45.26, 45.35, 212.49.

3-(1-methylethyl)-methylenecyclohexane (194). The following reagents were combined as described for **188**; NaH (0.72 g, 30 mmol) in DMSO (75 mL); methyltriphenylphosphonium iodide (12.12 g, 30 mmol) in DMSO (50 mL); and **193** (3.5 g, 25 mmol). After workup and distillation (bp_{58} 60-70 °C), 3.08 g **194** were recovered (89% yield); IR (Film) 3073, 2959, 2932, 2874, 2839, 1651, 1464, 1447, 1433 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.861 (d, J = 7 Hz, 3H), 0.864 (d, J = 7 Hz, 3H), 1.00-1.35 (m, 3H), 1.43 (oct, J = 7 Hz, 1H), 1.65-2.00 (m, 4H), 2.18-2.35 (m, 2H), 4.56-4.60 (m, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.72, 19.74, 27.50, 29.37, 32.59, 35.23, 38.72, 45.74, 106.65, 150.17.

3-(1-Methylethyl)-1-methylcyclohexane (195). A 25 mL flask was loaded with PtO_2 (50 mg), **194** (0.35 g, 2.5 mmol), and methanol (5 mL). The hydrogenation was carried out as in **189**. GC analysis determined the ratio of isomers to be 2.42:1 (trans:cis).

4-(1-Methylethyl)-methylenecyclohexane (196). The following reagents were combined as described for **188**; NaH (0.41 g, 17.1 mmol) in DMSO (17 mL); methyltriphenylphosphonium iodide (6.92 g, 17.1 mmol) in DMSO (40 mL); and **161** (1.94 g, 14.3 mmol). After workup and distillation (bp_{58} 60-70 °C), 1.64 g **196** was recovered (86% yield); IR (Film) 3073, 2963, 2874, 1651 cm^{-1}; ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (d, J = 7 Hz, 6H), 0.98-1.25 (m, 3H), 1.42 (oct, J = 7 Hz, 1H), 1.70-1.84 (m, 2H), 1.90-2.05 (m, 2H), 2.22-2.35 (m, 2H), 4.56 (t, J = 2 Hz, 2H); ^{13}C NMR (75 MHz) ($CDCl_3$) δ 19.84, 31.10, 32.39, 34.94, 43.66, 106.24, 150.31.

4-(1-Methylethyl)-1-methylcyclohexane (197). A 25 mL flask was loaded with PtO_2 (50 mg), **196** (0.35 g, 2.5 mmol), and methanol (5 mL). The hydrogenation was carried out as in **189**. GC analysis determined the ratio of isomers to be 2.23:1 (trans:cis).

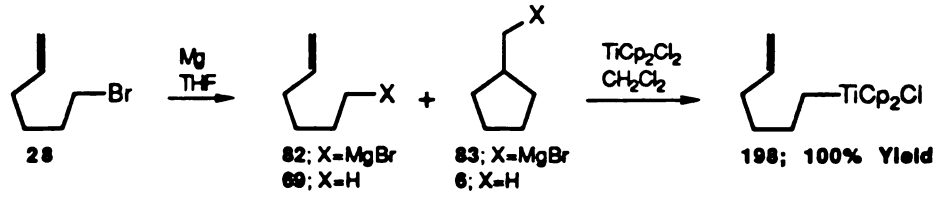
CHAPTER 2.

DIASTEREOSELECTIVE CYCLOPENTANE FORMATION MEDIATED BY TITANOCENE DICHLORIDE

1. Introduction

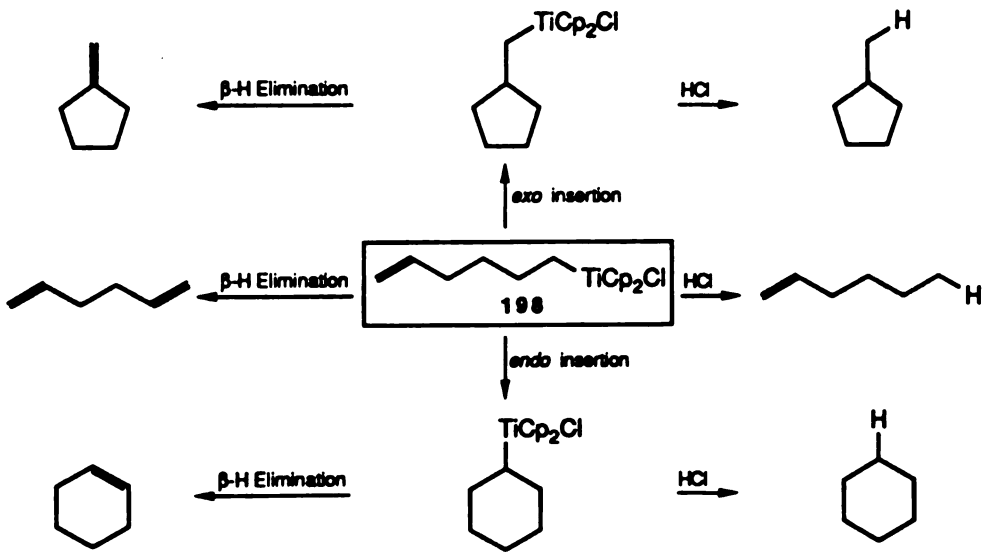
Our initial study began with the cyclization of a substrate utilized by Grubbs in an experiment previously described.[9a] Our intentions were to optimize the different steps in the linear sequence (Scheme 15), more accurately probe the regiocontrol of the olefin insertion, and determine the extent of β-elimination. Preparation of hex-5-en-1-yltitanocene chloride (**198**) utilized established procedures[6] in which bromide **28** was metallated by treatment with magnesium in THF (**82**, Scheme 26). Upon quenching an aliquot of **82** with an HCl/diethyl ether solution, the product mixture was determined to consist of a 95:5 ratio of 1-hexene (**69**) and methylcyclopentane (**6**). Furthermore, this ratio did not change upon continued heating. Transfer of the alkenyl ligand to titanium was accomplished with $TiCp_2Cl_2$ in CH_2Cl_2, which provided **198** in quanitative yield after purification.[69] It is noteworthy that the ratio of **69** to **6** did not change during the transmetallation process.

Scheme 26. Preparation of 5-Hexen-1-yltitanocene Chloride (198)



Scheme 27 represents the potential pathways that complex **198** could undergo. Treatment of **198** with a Lewis acid could result in simple destructive β-elimination to 1,5-hexadiene if the Lewis acid was too strong or the reaction temperature too high. On the other hand, if the conditions were too mild, **198** could be recovered unchanged. Upon fine tuning of the reaction conditions, productive bond formation could proceed in either an *exo* (five-membered ring formation) or an *endo* mode (six-membered ring formation). After cyclization, the alkyltitanocene complexes could presumably undergo β-elimination or, if stable to the reaction conditions, provide either methylcyclopentane or cyclohexane upon hydrolysis.

Scheme 27. Potential Pathways of Cyclization and Decomposition of 198



Treatment of a toluene solution of **198** with $EtAlCl_2$ (0.5-1.0 equiv) at -78 °C resulted in an immediate darkening of the mixture.[7a] This has been attributed to the complexation of the aluminum catalyst to the chloride on the titanium. The role of the aluminum was to either weaken or sever the titanium-chloride bond. The net result was the development of substantial positive charge on titanium, polarization the carbon-titanium bond, and to create an available coordination site for olefin complexation. Hydrolysis of the reaction mixture after 30-60 minutes revealed that complete consumption of **198** had occurred with concomitant formation of a single regioisomer, that of *exo* insertion. Yields of 85-95% (from **198**) were common for this insertion.[1b] Furthermore, no detectable amount of β-elimination was observed under the reaction conditions.

We have since reported a thorough investigation on the regiospecificity of 5-*exo*-trig olefin insertions with respect to structural differences of the olefin.[1a] A variety of vicinally and geminally substituted olefins, including systems where the olefin was either *endo*- or *exo*-cyclic in a ring and simple acyclic systems, were prepared and cyclized. In general, to promote complete cyclization, longer reaction times, higher temperatures, and higher catalyst concentrations were required. However, these factors had no effect on the yields or the regiospecificity of the reaction, the product of *exo* insertion was exclusively observed. A major consequence of the regiocontrol exhibited by this organometallic approach was the ease with which quaternary centers were produced, including geminal dimethyl and angular methyl groups, features which have proved troublesome by other methods.

In the present chapter, we report our findings regarding the effect a methyl group on the newly formed asymmetric center. In essence, could a respectable level of diastereomeric excess be achieved? In order to probe this question, we prepared and cyclized substrates analogous to hex-5-en-1-yltitanocene

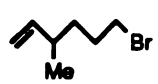
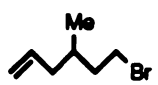
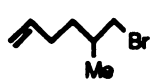
chlorides in which a methyl group was situated at the various positions on the tether. The titanium metal and its ligands were anticipated to have a strong influence on the stereochemistry of the product. First, as with other metals, titanium should be able to complex the olefin, thus restricting all four atoms into a syn-coplanar relationship, and thereby controlling the olefin geometry during bond formation. Secondly, in contrast to other ionic or radical methods, the ligands on the metal could have a pronounced effect on the geometrical deployment of the olefin and/or the alkyl group, and therefore exert more influence on the diastereomeric conformations in the transition state.

2. General Features and Limitations for the Synthesis of Methyl-Substituted 5-Hexen-1-yltitanocene Chlorides

Scheme 26 illustrates our chosen method for the preparation of the requisite alkenyltitanocene complexes. As already mentioned, reduction of the alkyl bromide with magnesium produced a small amount of cyclopentylmethyl magnesium bromide. This phenomena has been well documented by Ashby and others and has been explained in terms of single electron transfer (SET).[37] During this process, transient radical intermediates, thought to be formed in the reaction, underwent a rapid 5-*exo*-trig cyclization. This process presented no major problems for our model substrate since both radical cyclization and our titanocene-mediated method produced the same compound. However, for the substrates of interest in this chapter, SET was a menacing dilemma. Compounds **36a-d** cyclized to a much greater extent (12-21%) than did **27** (Table 2, Method A), presumably due to the Thorpe-Ingold substituent effect.[70] In contrast to **28**, **36a-d** produced a pair of diastereomers in a relatively indiscriminant fashion, which paralleled those for radical cyclization (Table 2, Method D). These shortcomings prompted a search for an alternative method of

Grignard formation. Rieke has developed a variety of methods to generate "active metals" which have been shown to metallate allylic and benzylic halides without dimerization.[71] We had hoped that rapid generation of the Grignard reagent at low temperatures with "active magnesium" may diminish cyclization at this stage. However, much to our dismay, we found only a marginal decrease in cyclization and a substantial decrease in the yield (Table 2, Method E).

Table 2. Diastereomer Ratios of Dimethylcyclopentane Products *via* Titanium and Free Radical Methods

Cyclization Precursor	Method[a]	Yield[b]	Uncyclized	Cyclopentane Products 1,2 (trans:cis)		1,3 (trans:cis)	
 (36a)	A	100	88	10	2		
	B	100	87	10	3		
	C	93	0	92	8		
	D	90	0	79	21		
	E	76	91.5	6.5	2		
 (36b)	A	98	83			3	14
	B	96	85			3	12
	C	93	0			3	97
	D	100	14			19	67
 (36c)	A	100	85			9	6
	B	64	77			14	9
	C	94	0			92	8
	D	88	0			59	41
 (36d)	A	86	79	7	12[c]		
	B	72	16	22	55[c]		
	D	85	17	19	64		
	E		81	2	7[c]		

[a]Method A: (1) Mg, THF, 45 °C. Method B: (1) Method A; (2) $TiCp_2Cl_2$, CH_2Cl_2. Method C: (1) Method A; (2) Method B; (3) 1.0 equiv. $EtAlCl_2$, Toluene, -78 °C; (4) HCl. Method D: AIBN, Bu_3SnH, C_6H_6, 80 °C. Method E: $MgCl_2$, K, THF, 0 °C. [b]Reference 69. [c]Balance of material consisted of three possible β-hydrogen elimination products.

Ligand transfer from magnesium to titanium provided two interesting results. Typically, no further cyclization occurred during the transmetallation process. However, an 8% increase was observed for **36c** (Table 2, Method B). When Grignard formation of **36c** was performed in diethyl ether, as opposed to THF, followed by transmetallation, 85-100% cyclization took place. Presumably

the less Lewis basic solvent, diethyl ether, did not complex the MgX_2 as tightly as THF, thereby allowing MgX_2 to promote the olefin insertion. Interestingly, MgX_2 was not an effective catalyst for the other substrates under these conditions. We are currently investigating the nature of this apparent rate enhancement for substrate **36c**. It is noteworthy that the α,β, and γ carbons to the titanium resemble the growing polyproylene chain in Ziegler-Natta polymerization, a system in which MgX_2 efficiently and stereoselectively catalyzed the polymerization of propylene. Secondly, ligand transfer of **36d** from magnesium to titanium resulted in almost complete cyclization, even in THF (Table 2, Method B). The similarity of the diastereomeric ratio formed to that observed for radical methods, suggest that radical ring closure occurred, not olefin insertion. It is not clear if the radical was produced by SET or by homolytic cleavage of the sterically crowded 2° carbon-titanium bond.

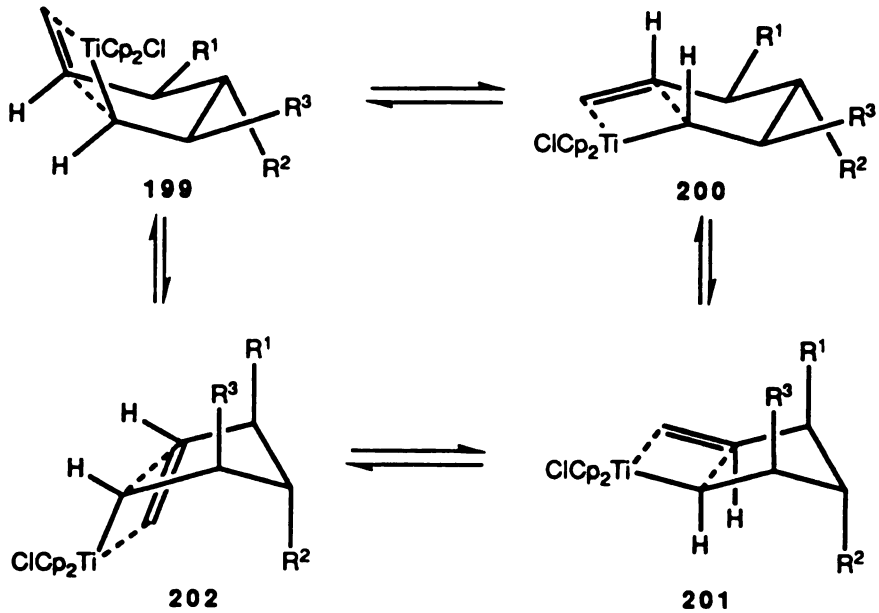
3. Synthesis and Cyclization of Methyl-Substituted 5-Hexen-1-yltitanocene Chlorides[1b]

Incorporation of a methyl group on the tether was found to have a significant effect on the stereochemical outcome of carbon-carbon bond formation. Treatment of the titanium complex of **36a** (Method C, Table 2) with $EtAlCl_2$, resulted in a 92:8 ratio (trans:cis) of 1,2-dimethylcyclopentanes. Taking into account the amount of cis isomer already present, a 94:6 diastereoselectivity during the Ziegler-Natta olefin insertion was realized. Similarily, **36b** underwent the Lewis acid assisted insertion which produced a 97:3 (cis:trans) diastereomeric mixture of 1,3-dimethylcyclopentanes. Thus, the actual diastereoselectivity was > 99:1. Finally, cyclization of the titanium complex of **36c** resulted in a high trans selectivity (92:8) and > 99:1 in the $EtAlCl_2$ step. The fact that titanium complexes of **36b** and **36c** yielded the same product selectivity

for different isomers, negates the possibility for product equilibration under the reaction conditions.

The stereoselectivity can be explained in terms of a psuedo-chair transition state (Scheme 28). Treatment of the organometallic complex with $EtAlCl_2$, resulted in complexation of the Lewis acidic aluminum to the chloride atom on the titanium.[7a] Although the extent of bond breaking of the titanium-chloride bond is unclear, the net result was distribution of substantial positive charge on titanium, increasing the electrophilicity of the metal, and weakening of the carbon-titanium bond. During olefin insertion, a four-centered transition state has been proposed in which the carbon-carbon double bond was assumed to be syn-coplanar with the carbon-titanium bond. Substantial stabilization would result from such an orientation based on orbital considerations previously described. Conformations **199-202** could accommodate such an interaction. However, in order to minimize eclipsing interactions, **199** and **202** would be strongly disfavored. Consequently, the diastereomeric ratio observed resulted from an unequal partitioning between **200** (major) and **201** (minor). Conformation **201** would be disfavored, with respect to **200**, since the methyl groups were axially deployed. Additional destabilization of an axial methyl group could arise from steric interactions with the cyclopentadienyl ligands on the metal.

Scheme 28. Proposed Transition States for Five-Membered Ring Formation

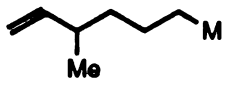
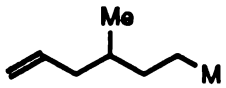
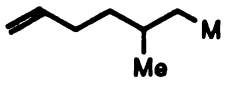


4. Comparison of the Stereoselective Outcome of Various Methods

With the variety of methods available to facilitate cyclization of the 5-hexen-1-yl system (Table 3), each having different steric and electronic characteristics at the activated carbon, some qualitative generalizations can be made about the factors that contribute to high stereoselectivities. Factors that deserve consideration include the nature of the reactive intermediate, ligands on the intermediate, and the temperature at which the reaction was conducted. In the case of radical cyclization (80 °C), selectivity drops off sharply as the methyl group was further removed from the olefin. Beckwith[17] and Houk[20] agree, based on independent calculations, that the major product was formed through a chair transition state in which the methyl group was in a pseudo equatorial position. As a point of divergency, Houk suggested that the conformation leading to the minor product resembled a boat transition state with the methyl group in an equatorial position, not a chair conformation with an axial methyl

group. In support of this, Houks calculations more accurately predict the relative ratio of products. The difference in energy between the two transition states (estimated to be 0.5 kcal/mol) was attributed to the closer proximity of the C_3 methylene (relative to the radical center) to the olefin. Examination of lithium cyclizations (-30 to 25 °C) revealed that excellent stereocontrol was realized for each substrate. In order to show that this drastic difference was not merely related to temperature, aluminum cyclizations are noted (67 °C). As in the case of lithium, excellent control over the newly formed asymmetric center was produced, despite the higher temperatures. Assuming Houk's model was an accurate description of the minor isomer, incorporation of the π complexing ability of the metal(s) into the transition state would increase the nonbonding interactions with the C_3 methylene and in turn, suppress the boat transition state. It can be seen by comparison of aluminum- and lithium-mediated cyclizations, that the ligands on aluminum had a subordinate role in the stereochemical outcome of bond formation. The minimal effect that the alkyl ligands on aluminum had on the stereoselectivity was likely a consequence of the sp^2 hybridization of aluminum, which directs the ligands away from the alkyl tether. Finally, cyclization mediated by titanium demonstrated the combined effects of π complexation, low temperatures (-78 °C), and proper geometry of the ligands for increased interactions with the alkyl tether. Thus, maximum stereocontrol was achieved.

Table 3. Comparison of Diastereoselectivities for Different Methods

Cyclization Precursor	M	Dimethycyclopentanes 1,2 (trans:cis)	1,3 (trans:cis)
	Radical	79:21	
	Li	97:3	
	$AlEt_2$	97:3	
	$TiCp_2Cl$	94:6	
	Radical		19:67
	Li		6:94
	$AlEt_2$		8:92
	$TiCp_2Cl$		1:99
	Radical		59:41
	Li		97:3
	$AlEt_2$		96:4
	$TiCp_2Cl$		99:1

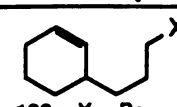
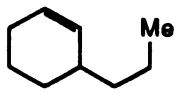
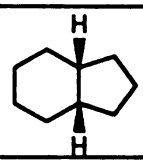
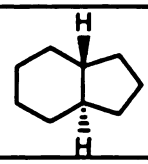
5. Optimization and Cyclization of 133: Formation of Bicyclo[4.3.0]nonane

Methodology directed toward the efficient formation of multiple ring products is an important transformation. With the advent of new reaction conditions to facilitate olefin insertion for our titanium approach, we were compelled to reinvestigate the cyclization of **133**.[1a,72] In this substrate, 5-*exo*-trig insertion into the vicinally substituted olefin presented new challenges compared to the other substrates in this chapter. The primary obstacle to be surmounted was bringing the sterically congested olefin into the titanocene wedge.

Table 4 illustrates some represenative conditions attempted for cyclization of **133b**. As previously shown for other vicinal olefins,[1a] $EtAlCl_2$ (entry 1) was ineffective at -78 °C. Since $EtAlCl_2$ was incompatible with **133b** at higher temperatures, recourse to other Lewis acids was necessary. Me_2AlCl was marginally successful in toluene (entry 2), providing a 54% recovery of material (combined yield of acyclic and cyclic). By simply changing the reaction medium

to CH_2Cl_2, reaction times were diminished and conversions were enhanced (entry 3).

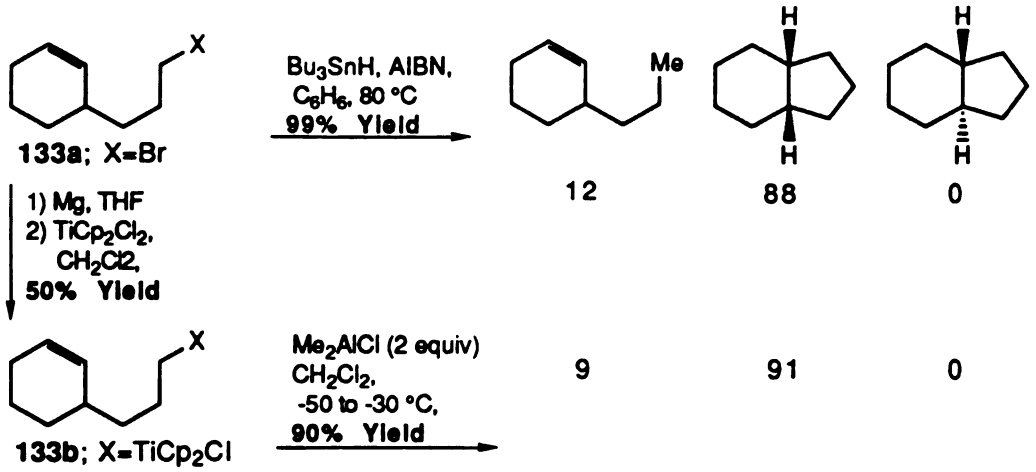
Table 4. Optimization of the Cyclization Conditions for 133b

 133a; X = Br 133b; X = $TiCp_2Cl$	% Yield[b]			
1) $EtAlCl_2$ (2 equiv.) Toluene, -78 °C	93	86	14	0
2) Me_2AlCl (1.5 equiv.) Toluene, -30 to -10 °C	54	23	77	0
3) Me_2AlCl (1.5 equiv.) CH_2Cl_2, -30 °C	59	10	90	0

[a](1) **133a**, Mg, THF, 45 °C; (2) $TiCp_2Cl_2$, **50% yield.** [b]**Reference 69.**

Scheme 29 depicts the comparison of radical and titanium-mediated cyclization of **133**. Conversion of **133** to **133b** was accomplished in the usual fashion, which resulted in a 50% yield after purification. Further optimization for the isolation of this complex is warranted. Treatment of **133b** under the optimized conditions resulted in the exclusive formation of the cis isomer in 82% yield. Similarily, treatment of **133** under the tin-hydride conditions produced the same stereoselectivity. Apparently, the highly rigid nature of this 5-hexen-1-yl analog precludes attack from the opposite face.

Scheme 29. Comparison of Titanium-Mediated Cyclization to Free Radical Cyclization for 133a



6. Conclusion

The results described in this chapter demonstrate a powerful new tool for stereoselective cyclopentane formation. Several general features about the efficiency and selectivity of the Ziegler-Natta insertion deserve mentioning. Activation of the hex-5-en-1-yltitanocene complexes with 0.5-1.0 equivalents of $EtAlCl_2$ facilitated complete cyclization within 30 minutes at -78 °C. Olefin insertion was completely regiospecific (*exo* cyclization) and the conditions did not produce detectable amounts of β-hydrogen elimination products. The elegance of this methodology was inherent in the ability of the titanium and its ligands to control the selectivity of carbon-carbon bond formation. In all cases, >94:6 diastereoselectivity was observed for the intramolecular olefin insertion with >90% yields achieved.

7. Experimental

Radical Cyclization of 6-Bromo-3-methyl-1-hexene (36a). A Schlenk flask was loaded with AIBN (10 mg), evacuated, purged with argon, and then benzene (10 mL) was added. Bromide **36a** (88.5 mg, 0.5 mmol) and Bu_3SnH (174.6 mg, 0.6 mmol) were added to the flask and the reaction mixture was heated to 80 °C for 8 hours. Analysis of the reaction mixture using gas chromatographic techniques[69] revealed that a 90% yield of *cis*- and *trans*-1,2-dimethylcyclopentanes (21:79, respectively) was obtained (see Table 2, Method D).

Radical Cyclization of 6-Bromo-4-methyl-1-hexene (36b). A Schlenk flask was loaded with AIBN (10 mg), evacuated, purged with argon, and then benzene (10 mL) was added. Bromide **36b** (88.5 mg, 0.5 mmol) and Bu_3SnH (174.6 mg, 0.6 mmol) were added to the flask and the reaction mixture was heated to 80 °C for 8 hours. Analysis of the reaction mixture (see Table 2, Method D)[69] showed the reaction resulted in a 100% yield of a mixture of 4-methyl-1-hexene (14%) and *cis*- and *trans*-1,3-dimethylcyclopentanes (86%, 78:22, respectively).

Radical Cyclization of 6-Bromo-5-methyl-1-hexene (36c). A Schlenk flask was loaded with AIBN (10 mg), evacuated, purged with argon, and then benzene (10 mL) was added. Bromide **36c** (88.5 mg, 0.5 mmol) and Bu_3SnH (174.6 mg, 0.6 mmol) were added to the flask and the reaction mixture was heated to 80 °C for 8 hours. Analysis of the reaction mixture using gas chromatographic techniques[69] revealed that an 88% yield of *cis*- and *trans*-1,3-dimethylcyclopentanes (41:59, respectively) was obtained (see Table 2, Method D).

Radical Cyclization of 6-Bromo-6-methyl-1-hexene (36d). A Schlenk flask was loaded with AIBN (10 mg), evacuated, purged with argon, and then benzene (10 mL) was added. Bromide **36d** (88.5 mg, 0.5 mmol) and Bu_3SnH (174.6 mg, 0.6 mmol) were added to the flask and the reaction mixture was heated to 80 °C for 8 hours. Analysis of the reaction mixture (see Table 2, Method D)[69] showed the reaction resulted in a combined yield of 85% of the following mixture: 1-heptene (17%) and *cis*- and *trans*-1,3-dimethylcyclopentanes (83%, 77:23, respectively).

Grignard Formation of 6-Bromo-3-methyl-1-hexene (36a) Using Rieke Magnesium. Potassium metal (70.4 mg, 2.18 mmol) and anhydrous $MgCl_2$ (95.21 mg, 1.00 mmol) were loaded into a Schlenk flask under an atmosphere of nitrogen and THF (4 mL) was added. The mixture was heated to reflux for 3 hours, cooled to 0 °C, and **36a** (88.45 mg, 0.5 mmol) was added. Analysis of the final mixture (see Table 2, Method E), after quenching with 1.0 M HCl/Et_2O (3 mL), showed that a combined yield of 76% of the following mixture was obtained: 3-methyl-1-hexene (92%) and *cis*- and *trans*-1,2-dimethylcyclopentanes (8%, 2:6, respectively).

Grignard Formation of 6-Bromo-6-methyl-1-hexene (36d) Using Rieke Magnesium. Potassium metal (70.4 mg, 2.18 mmol) and anhydrous $MgCl_2$ (95.21 mg, 1.00 mmol) were loaded into a Schlenk flask under an atmosphere of nitrogen and THF (4 mL) was added. The mixture was heated to reflux for 3 hours, cooled to 0 °C, and **36d** (88.45 mg, 0.5 mmol) was added. Analysis of the final mixture (see Table 2, Method E), after quenching with 1.0 M HCL/Et_2O (3 mL), showed that a combined yield of 76% of the following mixture was obtained: 1-heptene (81%), *cis*- and *trans*-1,2-dimethylcyclopentanes (9%, 2:7, respectively), and a mixture of acyclic β-hydrogen elimination products (10%).

General Procedure for Ziegler-Natta Cyclization: 6-Bromo-3-methyl-1-hexene (36a). A Schlenk flask was charged with Mg (195 mg, 8.0 mmol) and heated under vacuum with a heatgun for 30 minutes. After cooling to ambient temperature, the flask was purged with argon, THF (2 mL) was added, and the flask was then placed in a 45 °C oil bath. Bromide **36a** (353.8 mg, 2.0 mmol) was added with a gas-tight syringe over 6 hours, followed by stirring for an additional 4 hours. A separate Schlenk flask was loaded with $TiCp_2Cl_2$ (598 mg, 2.4 mmol), evacuated and purged with argon, the $TiCp_2Cl_2$ was suspended in CH_2Cl_2 (8 mL), and the flask was cooled to -45 °C. Transmetallation of the organic ligand was accomplished by addition of the Grignard intermediate to the titanocene dichloride solution *via* cannula (an additional 1 mL THF was used to rinse the Mg), stirred for 30 minutes at -45 °C, and warmed to ambient temperature for an additional 5 hours. After transmetallation, the mixture was concentrated to approximately 4 mL followed by purification of the organometallic complex by filtration to remove the excess $TiCp_2Cl_2$ and the Lewis acidic Grignard salts. Purification was accomplished by taking the solution up in toluene (5 mL) and hexane (5 mL), stirring for 10 minutes at room temperature, and then cooling to 0 °C for 10 minutes. The entire mixture was transferred *via* cannula into another Schlenk flask (the flask was previously evacuated and filled with argon as before) that was equipped with a glass frit and the solution was pulled through the frit under a slight vacuum. The solids were rinsed with additional toluene (3 x 10 mL) and filtered. Concentration of the reaction mixture *in vacuo* provided the alkyltitanocene complex as a red slurry, which was diluted with toluene (14 mL) and cooled to -78 °C. The precise composition of the reaction mixture, consisting of cyclic and acyclic alkyltitanocene complexes, is illustrated in Table 2 (Method B). A 1.8 M solution of $EtAlCl_2$ (2 mmol) was added to the alkyltitanocene solution over 10 minutes, the reaction mixture was stirred for 60 minutes at -78 °C, and finally

quenched with 1.0 M HCl/Et_2O (5 mL). Analysis of the final reaction mixture (Table 2, Method C) showed that a 93% overall yield from the bromide of *cis*- and *trans*-1,2-dimethylcyclopentanes (8:92, respectively) was obtained.

Ziegler-Natta Cyclization of 6-Bromo-4-methyl-1-hexene (36b). Bromide **36b** (353.8 mg, 2.00 mmol) was cyclized according to the general procedure described for **36a.** The precise composition of the reaction mixture prior to addition of $EtAlCl_2$, consisting of cyclic and acyclic alkyltitanocene complexes, is illustrated in Table 2 (Method B). Analysis of the final reaction mixture, after hydrolysis (Table 2, Method C), showed that a 78% overall yield from **36b** to *cis*- and *trans*-1,3-dimethylcyclopentanes (97:3, respectively) was obtained.

Ziegler-Natta Cyclization of 6-Bromo-5-methyl-1-hexene (36c). Bromide **36c** (353.8 mg, 2.00 mmol) was cyclized according to the general procedure described for **36a.** The precise composition of the reaction mixture prior to addition of $EtAlCl_2$, consisting of cyclic and acyclic alkyltitanocene complexes, is illustrated in Table 2 (Method B). Analysis of the final reaction mixture, after hydrolysis (Table 2, Method C), showed that a 61% overall yield from **36c** to *cis*- and *trans*-1,3-dimethylcyclopentanes (8:92, respectively) was obtained.

Ziegler-Natta Cyclization of 6-Bromo-6-methyl-1-hexene (36d). Bromide **36d** (353.8 mg, 2.00 mmol) was converted to the titanocene derivative as described in the general procedure. Analysis of the reaction mixture after transmetallation (Table 2, Method B) showed a complex mixture of products was obtained in 72% overall yield from bromide **36d**, which consisted of the following: *cis*-1,2-dimethylcyclopentane (55%), *trans*-1,2-dimethylcyclopentane (22%), 1-heptene (16%), 1,6-heptadiene (3%), and 1,5-heptadiene (4%, mixture of isomers).

CHAPTER 3.

DIASTEREOSELECTIVE CYCLOHEXANE FORMATION MEDIATED BY TITANOCENE DICHLORIDE

1. Introduction

Probing the limits of our carbocycle forming methodology, compelled us to investigate the regio- and stereochemical preferences for the cyclization of substituted 6-hepten-1-yltitanocene chlorides, leading to dialkylcyclohexanes. The potential impact of such a study would be significant, if successful, since few methods exist for such a transformation. We were concerned that the entropic factors that denied access to 6-*exo*-trig cyclizations for other methods may diminish the success of our pursuits. Our primary concerns were the possible repercussions posed by the increased tether length. The increased flexibility of the alkyl tether could provide access to the *endo* insertion pathway, or at least diminish the diastereomeric preference during carbon-carbon bond formation. Based on the intramolecular-intermolecular polymerization of 1,6-heptadiene, Marvel has provided convincing evidence that *endo* insertion was a minor consideration.[8a] The polymer which was obtained consisted of 1,3-dialkylcyclohexane monomer units, although the stereochemical details for this polymerization are undetermined. In our intramolecular Ziegler-Natta carbocyclization study, we found that the optimum conditions for cyclization were highly dependent on the structure of the substrate. However, by judicious choice

of solvent, Lewis acid, temperature, and concentration, each substrate could be efficiently cyclized to yield methylcyclohexane products.

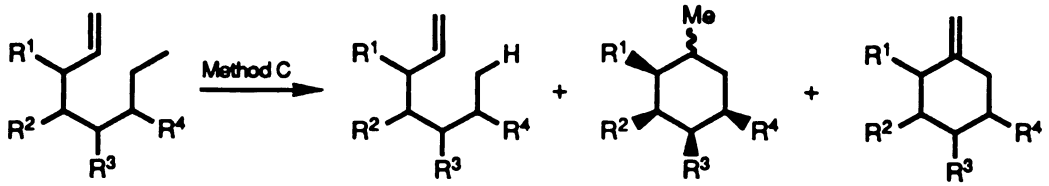
2. Optimization Studies for the Cyclization of 6-Hepten-1-yltitanocene Chlorides

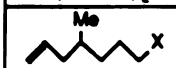
Synthesis of the various 6-hepten-1-yltitanocene complexes paralleled the method discussed previously with yields ranging from 75-100% (Method B, Table 5). A number of differences between the 5-hexen-1-yl and 6-hepten-1-yl systems are noted. First, although not surprising, no significant amount of cyclization resulting from SET could be detected during Grignard formation. This result was consistent with the fact that 6-*exo*-trig radical cyclizations were much slower ($k=5.4 \times 10^3\ s^{-1}$, 25 °C) than the corresponding 5-*exo*-trig ($k=2.3 \times 10^5\ s^{-1}$, 25 °C) cyclization.[17] This fact was emphasized by the low conversions (11-30%) obtained for the 7-bromo-1-heptene substrates when treated under the tin-hydride conditions (Table 5, Method A) used for the preparation of five-membered rings (Chapter 2). In most cases, transfer of the alkenyl ligand from magnesium to titanium did not cause further cyclization. However, in the case of **160**, 30-35% cyclization was observed during transmetallation when performed in the usual solvent (CH_2Cl_2). The extent of ligand cyclization could be controlled (10-20%) by use of toluene as a solvent. This cyclization phenomena paralleled that of **36c**, as both compounds contained an alkyl group β to the metal. These peculiarities will be the subject of Chapter 4. Finally, more forceful conditions were required to promote these cyclizations, which were found to be substrate dependent. For the sake of comparison, reaction times and Lewis acid concentrations increased from 30 minutes/1.0 equiv $EtAlCl_2$ to promote five-membered ring formation, to >150 minutes/>2.0 equiv $EtAlCl_2$ required for six-membered ring formation. What follows is a description of the various reaction

conditions used in order to achieve optimum conversion, yield, diastereoselectivity, and minimization of β-hydrogen elimination for each substrate.

Our optimization study was initiated by attempting the cyclization of the 6-hepten-1-yltitanocene chlorides using the conditions developed for cyclopentane formation (Table 5). Much to our delight, the first substrate chosen (**203b**) produced an 89% yield of cyclohexane products (Method C); no evidence of methylcycloheptane was observed. The reaction mixture consisted of a 76:17 (trans:cis) ratio of 1,3-dimethylcyclohexanes plus 5% 3-methyl-methylenecyclohexane (the product of β-hydrogen elimination). The amount of β-hydrogen elimination was dependent on the temperature at which the reaction was quenched, but even at -78 °C, approximately 5% β-hydrogen elimination was routinely observed. Treatment of **144b** under the conditions of Method C resulted in complete conversion (85% yield) to 1,2-dimethylcyclohexanes with excellent stereocontrol (>99:1, trans:cis). In this case, no evidence of β-elimination was seen. Similarly, activation of **151b** with $EtAlCl_2$ (Method C) produced a 79% yield of 1,3-dimethylcyclohexanes in >98:2 selectivity favoring the cis isomer. At this juncture, the only modification required of the previous cyclization conditions was an increase in reaction times. However, treatment of **155b** under these conditions produced only 25% cyclization. Because the uncyclized material coincided with the solvent peak by gas chromatographic analysis, we could not determine if the low yield of cyclohexane products was due to incomplete cyclization or some unknown side reaction. Moreover, low conversions were also observed for the cyclizations of **160b** and **137b** (56% and 27%, respectively).

Table 5. Diastereomer Ratios of Cyclohexane Products *via* Titanium and Free Radical Methods



Cyclization Precursor	Method[a]	Yield[b]	Uncyclized[c]	Methyl-cyclohexane	Dialkylcyclohexane Products		
					1,2 (t:c)	1,3 (t:c)	1,4 (t:c)
	A	84[d]	84		8:5		
144a; X = Br	B	100	99		1:1		
144b; X = $TiCp_2Cl$	C	85	0		99:1		
	A	90[d]	81			7:10	
151a; X = Br	B	100	100			0:0	
151b; X = $TiCp_2Cl$	C	79	0			2:98	
	A	75[d]	66				20:11
155a; X = Br	B	95	99				1:1
155b; X = $TiCp_2Cl$	C	25	e				71:29
	A	88[d]	83			7:9	
203a; X = Br	B	100	96			2:2	
203b; X = $TiCp_2Cl$	C	89[e]	2			76:17	
	A	88	70			10:20	
160a; X = Br	B	75	64			13:23	
160b; X = $TiCp_2Cl$	C	95[e]	41			31:28	
	A	95[f]	89	10			
137a; X = Br	B	73	99	1			
137b; X = $TiCp_2Cl$	C	51	48	52			

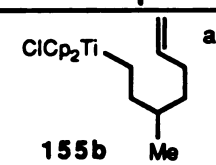
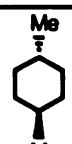
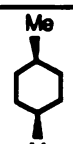
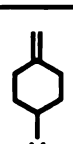
[a]Method A: AIBN, Bu_3SnH, C_6H_6, 80 °C. Method B: (1) Mg, THF, 45 °C, (2) $TiCp_2Cl_2$, CH_2Cl_2. Method C: (1) Method B, (2) 1.2 equiv. $EtAlCl_2$, Toluene, -78 °C, (3) HCl/ether. [b]Reference 69. [c]Numbers represent molar percent. [d]Methylcycloheptane (3%) was produced. [e] β-Hydrogen elimination (5-10%) was produced. [f]Cycloheptane (1%) was produced.

Entropic factors were certainly responsible for the slower cyclizations and possibly the decreased yields for certain 6-*exo*-trig cyclization substrates. The greater flexibility of the alkyl tether apparently diminished the ability of the olefin to become properly aligned with the carbon-titanium bond. This being the case, intermolecular insertions may supersede intramolecular insertions under these conditions. Since the transition state geometry was unclear, the non-bonding interactions experienced by the alkyl group may be more detrimental for the 6-*exo*-trig cyclization, thus retarding cyclization. The following conditions were systematically varied in order to attenuate intra- versus intermolecular events: (1) concentration (0.01-0.06 M), (2) different solvents of greater polarity, and (3) investigation of higher temperatures. Polar solvents were investigated in an attempt to increase the solubility of the organometallic complex, and to aid in the stabilization of polar intermediates.[7a] Both of these factors could help to increase the rate of cyclization. Higher temperatures were explored to surmount these entropic and/or steric activation barriers.

Table 6 illustrates a number of conditions used to facilitate the cyclization of **155b**. When temperatures higher than -78 °C were used, Me_2AlCl was the Lewis acid employed since $EtAlCl_2$ was shown to destroy the starting organometallic complex under these conditions. Entry 1 demonstrated that, in less than 140 minutes at -30 °C, three cyclohexane products were accounted for in 93% yield . The excessive amount of β-hydrogen elimination (34%) made it impossible to determine the selectivity. However, achieving complete conversion for this substrate was gratifying enough at that moment. In an attempt to decrease the amount of methylenecyclohexane produced, cyclization was conducted -50 °C. However, the reaction was substantially slower at this temperatute (26% cyclization, entry 3). When CH_2Cl_2 was used as the solvent under otherwise identical conditions (entry 2), a significant enhancement in the

conversion was observed (76% yield) with a concomitant decrease in the β-hydrogen elimination product (compare entries 1 and 3). Cyclization with Me_2AlCl at -78 °C could not be induced in CH_2Cl_2. However, encouraging results were realized with $EtAlCl_2$ under these conditions (entry 4). Although the yield of cyclized material was only 55%, 20% uncyclized material was still present. An increase in reaction time or Lewis acid concentration may help drive this reaction to completion. Under these conditions, selectivity was not observed.

Table 6. Optimization of the Cyclization Conditions for 155b

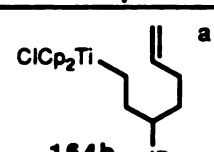
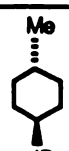
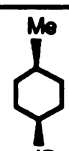
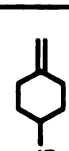
 155b	time (min)	uncyclized[b]				% Yield[c] (cis:trans)
1) Me_2AlCl (1.5 equiv.), Toluene, -30 °C, Molarity = 0.04 M	0	0.98	0.02	0.00	0.00	
	140	d	0.31	0.28	0.34	93
2) Me_2AlCl (1.5 equiv.), CH_2Cl_2, -50 °C, Molarity = 0.04 M	0	0.98	0.02	0.00	0.00	
	130	d	0.36	0.33	0.08	76 (50:50)
3) Me_2AlCl (1.5 equiv.), Toluene, -50 °C, Molarity = 0.04 M	0	0.98	0.02	0.00	0.00	
	180	d	0.12	0.10	0.04	26 (50:50)
4) $EtAlCl_2$ (1.8 equiv.), CH_2Cl_2, -78 °C, Molarity = 0.04 M	0	0.98	0.02	0.00	0.00	
	205	0.20	0.25	0.27	0.03	55 (52:48)

[a] (1) 155a, Mg, THF, 45 °C, (2) $TiCp_2Cl_2$, CH_2Cl_2. [b]Numbers represent millimolar ratios scaled to 1 for time=0 and percentage for the final time. [c]Reference 69. [d] Can't be determined because the peak for this product coincides with the solvent peak.

Due to the lack of selectivity encountered for cyclization of **155b**, we were interested in seeing what effect a larger alkyl group would have on the diastereoselectivity of bond formation. Table 7 illustrates the results for **164b**. As before, excellent conversion occurred at -30 °C with Me_2AlCl (entry 1) yet β-

hydrogen elimination (22%) was the fate of a substantial portion of the cyclohexylmethyltitanocene intermediates under the reaction conditions. The longer reaction time in this case was due to the concentration of the reaction. Similar yields were obtained under the conditions of entry 2 with the usual decrease in β-hydrogen elimination. As opposed to the substrate with a corresponding methyl group in this position (**155b**), **164b** underwent facile and efficient cyclization in toluene at -78 °C (entry 4). More importantly, a 74:26 (cis:trans) ratio of 1-(1-methylethyl)-4-methylcyclohexanes was produced.

Table 7. Optimization of the Cyclization Conditions for 164b

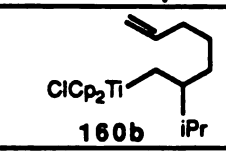
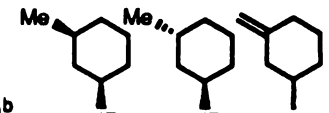
 **164b**	time (min)	uncyclized[b]				% Yield[c] (cis:trans)
1) Me_2AlCl (1.0 equiv.), Toluene, -30 °C, Molarity = 0.02 M	0	0.97	0.02	0.01	0.00	
	390	0.10	0.28	0.27	0.22	77
2) Me_2AlCl (1.5 equiv.), CH_2Cl_2, -50 °C, Molarity = 0.05 M	0	0.94	0.04	0.02	0.00	
	120	0.03	0.25	0.37	0.15	77
3) $EtAlCl_2$ (1.5 equiv.), CH_2Cl_2, -78 °C, Molarity = 0.05 M	0	0.94	0.04	0.02	0.00	
	150	0.14	0.18	0.50	0.02	69 (74:26)
4) $EtAlCl_2$ (1.5 equiv.), Toluene, -78 °C, Molarity = 0.04 M	0	0.97	0.02	0.01	0.00	
	150	0.00	0.18	0.52	0.12	82 (74:26)

[a](1) **164a**, Mg, THF, 45 °C, (2) $TiCp_2Cl_2$, CH_2Cl_2. [b]Numbers represent millimolar ratios scaled to 1 for time=0 and percentage for the final time. [c]Reference 69.

The conditions developed for **155b** were applied to **160b** with the results shown in Table 8. Entry 1 shows that high conversions were possible with a bulky isopropyl group near the metal center. A 79% yield of three cyclohexane products was observed with 35% β-hydrogen elimination as before. Changing

solvents and decreasing the reaction temperature (entry 2) resulted in a 68% yield and a marked decrease in β-hydrogen elimination. Finally, cyclization in CH_2Cl_2 at -78 °C (entry 3) resulted in low conversions (<55%), but the diastereoselectivity was >99:1 during the Ziegler-Natta insertion reaction.

Table 8. Optimization of the Cyclization Conditions for 160b

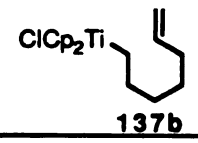
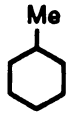
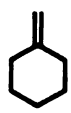
 160b	time (min)	uncyclized[b]		% Yield[c] (cis:trans)
1) Me_2AlCl (1.5 equiv.), Toluene, -30 °C, Molarity = 0.07 M	0	0.93	0.05 0.02 0.00	
	180	0.04	0.15 0.30 0.34	79
2) Me_2AlCl (1.5 equiv.), CH_2Cl_2, -50 °C, Molarity = 0.04 M	0	0.69	0.20 0.11 0.00	
	300	0.07	0.29 0.27 0.11	68
3) $EtAlCl_2$ (1.5 equiv.) Toluene, -78 °C, Molarity = 0.04 M	0	0.69	0.20 0.11 0.00	
	150	0.28	0.20 0.31 0.05	84 (1:99)

[a](1) 160a, Mg, THF, 45 °C, (2) $TiCp_2Cl_2$, Toluene. [b]Numbers represent millimolar ratios scaled to 1 for time=0 and percentage for the final time. [c]Reference 69.

Finally, Table 9 contains the results for the cyclization of **137b**. Since alkyl substituents were absent on the tether, this substrate was expected to cyclize even more slowly than the other 6-hepten-1-yl substrates. Under the conditions for the 5-*exo*-trig cyclization, only 27% cyclization occurred along with 24% uncyclized material (Table 5). Once again, entry 1 showed that high yields and conversions were possible at higher temperatures but a large amount of β-elimination rendered these conditions useless. A decrease in the concentration (0.044 M vs 0.124 M) resulted in a marked enhancement in conversion, yet only a 56% yield of methylcyclohexane was produced. An increase in the polarity of the reaction medium (entries 4 and 5) revealed that moderate yields but good conversions were possible at -78 °C. To combat the intermolecular insertions,

which were probably responsible for the low yields, substantially lower concentrations were warranted.

Table 9. Optimization of the Cyclization Conditions for 137b

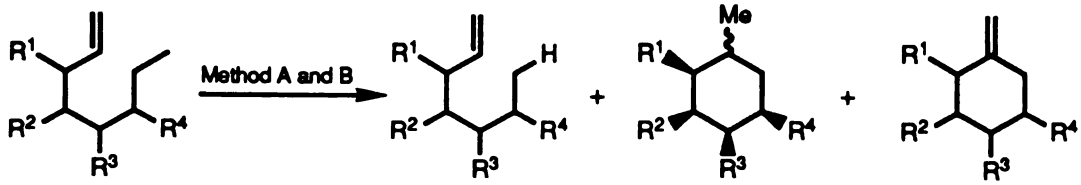
 137b	time (min)	uncyclized[b]			% Yield[c]
1) Me_2AlCl (1.5 equiv.), Toluene, -30 °C Molarity = 0.05 M	0	0.99	0.01	0.00	
	125	0.04	0.71	0.19	90
2) $EtAlCl_2$ (1.5 equiv.) Toluene, -78 °C Molarity = 0.12 M	0	0.99	0.01	0.00	
	210	0.24	0.27	0.00	41
3) $EtAlCl_2$ (2.0 equiv.), Toluene, -78 °C Molarity = 0.04 M	0	0.98	0.02	0.00	
	120	0.00	0.56	0.00	56
4) $EtAlCl_2$ (1.5 equiv.), -78 °C Toluene:CH_2Cl_2 (1:1) Molarity= 0.03 M	0	0.98	0.02	0.00	
	150	0.04	0.64	0.00	64
5) 1.2 eq $EtAlCl_2$ (1.2 equiv.), CH_2Cl_2, -78 °C Molarity = 0.04 M	0	0.98	0.02	0.00	
	105	0.07	0.52	0.00	52

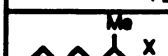
[a](1) **137a**, Mg, THF, 45 °C (2) $TiCp_2Cl_2$, CH_2Cl_2. [b]Numbers represent millimolar ratios scaled to 1 for time=0 and percentage for the final time. [c]Reference 69.

With optimal conditions obtained for each substrate, attention was focused on performing these cyclizations on a synthetically more useful scale.[1c] Synthesis of the requisite 6-hepten-1yltitanocene complexes was accomplished without incident (Table 10, Method A). Activation of **137b** with $EtAlCl_2$ under high dilution conditions (0.01 M, CH_2Cl_2, -78 °C), resulted in exclusive *exo* cyclization to provide methylcyclohexane in modest yield (76% yield). Cyclization of **144b** and **151b** were efficiently achieved under much more concentrated conditions (0.12 M, toluene, -78 °C) and provided essentially a

single stereoisomer in each case, 99:1 and 3:97 (trans:cis), respectively. Although the γ-methyl group of **155b** had no bearing on the selectivity of bond formation (50:50), the increased steric demands of the isopropyl group of **164b** significantly enhanced the production of the cis diastereomer (trans:cis, 23:77), with a paralleled increase in yield (91%). Cyclization of **203b** and **160b** were unique compared to the others, as β-elimination seemed to be a more accessible pathway (9% in each case). Compound **203b** showed a useful preference for the trans isomer (81:19). Metallation of **160a** with magnesium provided a high yield of the Grignard intermediate with no evidence of cyclization. However, transfer of the alkenyl ligand to titanium resulted in 17% cyclization, even with THF present. The most interesting observation was that MgX_2 was selective for the opposite isomer (trans:cis, 1:2) than produced with an aluminum cocatalyst. Cyclization of **160b** provided three cyclohexane products (71:18:9). If the extraordinary amount of cyclization that transpired during transmetallation was factored out, a 92:8 preference for the *trans* isomer was produced during the Ziegler-Natta olefin insertion process.

Table 10. Diastereomer Ratios of Cyclohexane Products Performed Under the Optimized Conditions



Cyclization Precursor	Method[a]	Yield[b]	Uncyclized[c]	Methyl-cyclohexane	Dialkylcyclohexanes		
					1,2 (c:t)	1,3 (c:t)	1,4 (c:t)
							
137a X = Br	A	73	99	1			
137b X = $TiCp_2Cl$	B	76	3	97			
							
144a X = Br	A	e	98		2:0		
144b X = $TiCp_2Cl$	B	89	<1		99:1		
							
151a X = Br	A	82	97			0:3	
151b X = $TiCp_2Cl$	B	91	<1			3:97	
							
155a X = Br	A	65	97				2:1
155b X = $TiCp_2Cl$	B[d]	63	<1				50:50
							
164a X = Br	A[f]	50	97				2:1
164b X = $TiCp_2Cl$	B	91	3				23:77
							
203a X = Br	A	97	96			2:2	
203b X = $TiCp_2Cl$	B	72[g]	2			74:17	
							
160a X = Br	A	74	83			6:11	
160b X = $TiCp_2Cl$	B[d]	88[g]	2			71:18	

[a]Method A: (1) Bromide, Mg, THF, 45 °C, (2) $TiCp_2Cl_2$, CH_2Cl_2. Method B: (1) 1.75-2.25 equiv. $EtAlCl_2$, Toluene, -78 °C, (3) HCl/ether. [b]Reference 69. [c]Numbers represent ratios scale to 100. [d]CH_2Cl_2 was used as a solvent. [e]Could not be determined. Final yield calculated from the bromide. [f]Toluene was used as a solvent. [g]β-Hydrogen elimination (9%) was observed.

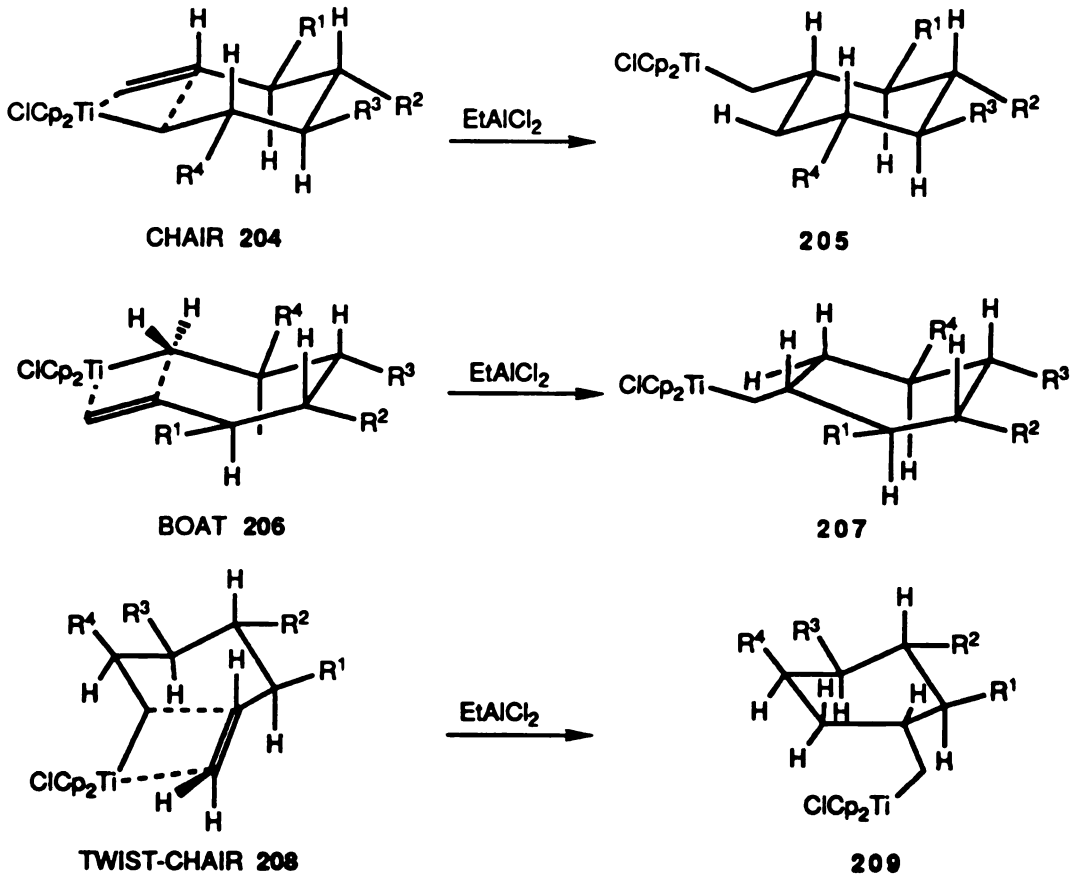
These results illustrate for the first time a useful method to affect 6-*exo*-trig cyclizations into unactivated alkenes with synthetically satisfying selectivities. In addition, a number of useful pieces of information have been acquired about the Ziegler-Natta process by examination of the alkene facial selectivity of a single insertion. A methyl group was shown to have a pronounced effect during the syn-coplanar insertion for **144b** and **151b**. In contrast, the presence of the methyl group γ to the metal (**155b**) had no bearing at all on the stereogenicity of the new asymmetric center. These results paralleled those of the polymerization of racemic or optically active α-olefins.[73] For example, 3-methyl-1-pentene and 4-methyl-1-hexene induced a high degree of stereoselection during polymerization, yet 5-methyl-1-heptene had little effect on the facial selectivity. The stereochemical outcome for the cyclization of **203b**, provided evidence that the polymerization of 1,6-heptadiene contained primarily a trans 1,3 relationship. Finally, the stereoselective divergence between the different cocatalysts, MgX_2 and $EtAlCl_2$, suggested that the catalyst-cocatalyst interaction is more sophisticated than simple generation of $[Cp_2TiR^+]$.

3. Potential Explanations for the Observed Stereoselectivities

By examination of molecular models, three possible transition states for cyclization seemed reasonable. Scheme 30 illustrates these possibilities: chair (**204**), boat (**206**), and twist-chair (**208**). Each transition state allowed for the alkyl groups to be directed in psuedo-equatorial positions to minimize unfavorable non-bonding interactions. The chair transition state was less likely since the desirable syn-coplanar alignment of the olefin and the carbon-titanium bond was precluded. The boat and twist-chair conformations were able to accommodate this transition state requirement. Severe eclipsing interactions

between the substituents at the β and γ positions (relative to titanium) may tend to disfavor the boat transition state. Examination of the products formed from the substrates with various substitution patterns on the alkyl tether, however, did not allow for differentiation between the boat and the twist-chair. Both conformations accurately predicted the major product for substitution at the allylic and homoallylic sites. The apparent similarity between the steric environment surrounding the β and γ positions suggested that a methyl substituent would have similar effects in both cases. However, γ-methyl substitution produced no selectivity. Differences in selectivity between the β- and γ-methyl compounds was attributed to the increased steric interactions at the β-position due to the closer proximity to the congested metal center. The steric environment created by the cyclopentadienyl ligands on titanium and the Lewis acid-chloride-titanium complex strongly influenced the axial or equatorial orientation of neighboring alkyl groups.

Scheme 30. Possible Transition States for Six-Membered Ring Formation



4. Conclusion

The results in this chapter describe a powerful new method for the construction of six-membered rings. This method represents the most successful procedure to affect 6-*exo*-trig cyclization from an sp^3 carbon with an unactivated alkene. The need for a syn-coplanar orientation of the alkene and the carbon-titanium bond had a significant impact on the regio- and stereoselectivity. Olefin insertion was found to proceed with complete *exo* specificity, which resulted in the formation of a new asymmetric center. In most cases, an alkyl group induced a high degree of alkene facial selectivity, providing synthetically useful diastereomeric excesses. Although a single general procedure was not

realized, a variety of new conditions were developed along the way which will provide additional avenues to affect the desired bond construction. This method furnishes the synthetic chemist with another useful tool for the construction of five- and six-membered rings with the high degree of stereocontrol demanded by today's complex synthetic targets.

5. Experimental

Radical Cyclization of 7-Bromo-1-heptene (137a). The following reagents were combined and heated to 80 °C in a sealed tube for 10 hours: bromide **137a** (88.5 mg, 0.5 mmol), AIBN (10 mg), Bu_3SnH (174.6 mg, 0.6 mmol), and benzene (10 mL). Analysis of the reaction mixture (see Table 5, Method A)[69] indicated that a combined yield of 96% was obtained which consisted of the following compounds: 1-heptene (89%), methylcyclohexane (10%), and cycloheptane (1%).

Radical Cyclization of 7-Bromo-3-methyl-1-heptene (144a). The following reagents were combined and heated to 80 °C in a sealed tube for 10 hours: bromide **144a** (95.5 mg, 0.5 mmol), AIBN (10 mg), Bu_3SnH (174.6 mg, 0.6 mmol), and benzene (10 mL). Analysis of the reaction mixture (see Table 5, Method A)[69] indicated that a combined yield of 84% was obtained which consisted of the following compounds: 3-methyl-1-heptene (84%), *cis*- and *trans*-1,2-dimethylcyclohexanes (13%, 5:8, respectively), and methylcycloheptane (3%).

Radical Cyclization of 7-Bromo-4-methyl-1-heptene (151a). The following reagents were combined and heated to 80 °C in a sealed tube for 10 hours: bromide **151a** (95.5 mg, 0.5 mmol), AIBN (10 mg), Bu_3SnH (174.6 mg, 0.6 mmol), and benzene (10 mL). Analysis of the reaction mixture (see Table 5, Method A)[69] indicated that a combined yield of 90% was obtained which consisted of the following compounds: 4-methyl-1-heptene (81%), *cis*- and *trans*-1,3-dimethylcyclohexanes (17%, 10:7, respectively), and methylcycloheptane (2%).

Radical Cyclization of 7-Bromo-5-methyl-1-heptene (155a). The following reagents were combined and heated to 80 °C in a sealed tube for 10 hours: bromide **155a** (95.5 mg, 0.5 mmol), AIBN (10 mg), Bu_3SnH (174.6 mg, 0.6

mmol), and benzene (10 mL). Analysis of the reaction mixture (see Table 5, Method A)[69] indicated a combined yield of 75% was obtained which consisted of the following compounds: 5-methyl-1-heptene (66%), *cis*- and *trans*-1,4-dimethylcyclohexanes (31%, 11:20, respectively), and methylcycloheptane (3%).

Radical Cyclization of 7-Bromo-6-methyl-1-heptene (203a). The following reagents were combined and heated to 80 °C in a sealed tube for 10 hours: bromide **203a** (95.5 mg, 0.5 mmol), AIBN (10 mg), Bu_3SnH (174.6 mg, 0.6 mmol), and benzene (10 mL). Analysis of the reaction mixture (see Table 5, Method A)[69] indicated a combined yield of 84% was obtained which consisted of the following compounds: 6-methyl-1-heptene (83%), *cis*- and *trans*-1,3-dimethylcyclohexanes (16%, 9:7, respectively), and methylcycloheptane (1%).

Radical Cyclization of 7-Bromo-6-(1-methylethyl)-1-heptene (160a). The following reagents were combined and heated to 80 °C in a sealed tube for 10 hours: bromide **160a** (110 mg, 0.5 mmol), AIBN (10 mg), Bu_3SnH (174.6 mg, 0.6 mmol), and benzene (10 mL). Analysis of the reaction mixture (see Table 5, Method A)[69] indicated a combined yield of 88% was obtained which consisted of the following compounds: 6,7-dimethyl-1-octene (70%), *cis*- and *trans*-1-(1-methylethyl)-3-methylcyclohexanes (30%, 20:10, respectively).

General Procedure for Ziegler-Natta Cyclization for 7-Bromo-1-heptene Substrates: A Schlenk flask was charged with Mg (195 mg, 8 mmol) and flame-dried under vacuum. After cooling to ambient temperature, the flask was purged with argon, THF (2 mL) was added, and the flask was then placed in a 45 °C oil bath. The bromide (2 mmol) was added to the magnesium with a gas-tight syringe over 6 hours, followed by stirring for an additional 4 hours. A separate Schlenk flask was loaded with $TiCp_2Cl_2$ (598 mg, 2.4 mmol), evacuated and purged with argon, the $TiCp_2Cl_2$ was suspended CH_2Cl_2 (8 mL), and the flask was cooled to -45 °C. Transmetallation was accomplished by adding the Grignard

reagent to the $TiCp_2Cl_2$ suspension *via* cannula (an additional 1 mL THF was used to rinse the Mg), stirring for 30 minutes at -45 °C, and warming to ambient temperature where the reaction mixture remained for an additional 5 hours. After transmetallation was complete, the mixture was concentrated to approximately 4 mL, taken up in toluene (5 mL) and hexane (5 mL), stirred for 10 minutes at room temperature, and then cooled to 0 °C for 10 minutes. The entire mixture was transferred *via* cannula and filtered under argon through a glass frit. The solids were rinsed with additional toluene (3 x 10 mL) and filtered. Removal of the solvents *in vacuo* left behind the organotitanocene chloride as a red slurry. Toluene was then added and the solution was cooled to -78 °C. In general, $EtAlCl_2$ was added to the alkyltitanocene chloride solution by three sequential additions over a period of 90 minutes. When the reaction was complete, 1.0 M HCl/Et_2O (10 mL) was added at -78 °C to quench the reaction.

General Procedure for the Optimization of Cyclization Conditions. Preparation of the alkyltitanocene chloride complex was the same as described in the general procedure unless otherwise stated. Typically, 2 mL of the alkyltitanocene chloride complex was added to a flame-dried flask, diluted to the desired molarity, and cooled to the appropriate temperature. The Lewis acid to be used was added over 10-15 minutes and the progress of the reaction was monitored by gas chromatography. For optimization results for specific substrates, see the following tables: Table 6 (**155b**), Table 7 (**164b**), Table 8 (**160b**), and Table 9 (**137b**).

Ziegler-Natta Cyclization of 7-Bromo-1-heptene (137a). Bromide **137a** (353.8 mg, 2.0 mmol) was converted to alkyltitanocene **137b** in 73% yield following the general procedure. The product mixture prior to addition of the cocatalyst consisted of 1-heptene and methylcyclohexane (99:1), respectively (see Table 10, Method A). The titanium residue, after filtration and evaporation of

solvents, was diluted with toluene (200 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added sequentially as follows: 1.0 equiv. (t=0 min), 0.75 equiv. (t=45 min), and 0.50 equiv. (t=90 min). Analysis of the final reaction mixture after hydrolysis (Table 10, Method B) showed that a 76% yield for the Lewis acid assisted insertion (56% yield from the bromide) was obtained which consisted of the following compounds: methylcyclohexane (97%), heptene (3%), and methlyenecyclohexane (0%).

Ziegler-Natta Cyclization of 7-Bromo-3-methyl-1-heptene (144a). Bromide **144a** (381.8 mg, 2.0 mmol) was converted to alkyltitanocene **144b** according to the general procedure. The product mixture prior to addition of the cocatalyst consisted of 3-methyl-1-heptene and *cis*- and *trans*-1,2-dimethylcyclohexanes (98:2:0), respectively (see Table 10, Method A). The titanium residue, after filtration and evaporation of solvents, was diluted with toluene (15 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added sequentially as follows: 1.0 equiv. (t=0 min), 0.75 equiv. (t=45 min), and 0.50 equiv. (t=90 min). Analysis of the final reaction mixture (Table 10, Method B), after hydrolysis, showed that an 89% yield overall from the bromide was obtained which consisted of the following compounds: *trans*-1,2-dimethylcyclohexane (98%), *cis*-1,2-dimethylcyclohexane (1%), and 2-methyl-1-methlyenecyclohexane (<1%).

Ziegler-Natta Cyclization of 7-Bromo-4-methyl-1-heptene (151a). Bromide **151a** (353.8 mg, 2.0 mmol) was converted to alkyltitanocene **151b** in 82% yield following the general procedure. The product mixture prior to addition of the cocatalyst consisted of 4-methyl-1-heptene and *cis*- and *trans*-1,3-dimethylcyclohexanes (97:0:3), respectively (see Table 10, Method A). The titanium residue, after filtration and evaporation of solvents, was diluted diluted toluene (15 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added

sequentially as follows: 1.0 equiv. (t=0 min), 0.75 equiv. (t=45 min), and 0.50 equiv. (t=90 min). Analysis of the final reaction mixture after hydrolysis (Table 10, Method B) showed that a 91% yield for the Lewis acid assisted insertion (75% yield from the bromide) was obtained which consisted of the following compounds: *trans*-1,3-dimethylcyclohexane (3%), *cis*-1,3-dimethylcyclohexane (97%), and 3-methyl-1-methlyenecyclohexane (<1%).

Ziegler-Natta Cyclization of 7-Bromo-5-methyl-1-heptene (155a). Bromide **155a** (353.8 mg, 2.0 mmol) was converted to alkyltitanocene **155b** in 65% yield following the general procedure. The product mixture prior to addition of the cocatalyst consisted of 5-methyl-1-heptene and *cis*- and *trans*-1,4-dimethylcyclohexanes (97:2:1), respectively (see Table 10, Method A). The titanium residue, after filtration and evaporation of solvents, was diluted with CH_2Cl_2 (45 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added sequentially as follows: 1.0 equiv. (t=0 min), 0.75 equiv. (t=45 min), and 0.50 equiv. (t=90 min). Analysis of the final reaction mixture after hydrolysis (Table 10, Method B) showed that a 63% yield for the Lewis acid assisted insertion (41% yield from the bromide) was obtained which consisted of the following compounds: *trans* -1,4-dimethylcyclohexane (50%), and *cis*-1,4-dimethylcyclohexane (50%). No detectable amount of 4-methyl-1-methlyenecyclohexane or 5-methylhept-1-ene was observed.

Ziegler-Natta Cyclization of 7-Bromo-5-(1-methylethyl)-1-heptene (164a). Bromide **164a** (218.9 mg, 1.0 mmol) was converted to alkyltitanocene **164b** in 50% yield following the general procedure. The product mixture prior to addition of the cocatalyst consisted of 5-ethyl-6-methyl-1-heptene and *cis*- and *trans*-1,4-isopropylcyclohexanes (97:2:1), respectively (see Table 10, Mehtod A). The titanium residue, after filtration and evaporation of solvents, was diluted with toluene (12 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added

sequentially as follows: 1.0 equiv. (t=0 min), 0.75 equiv. (t=45 min), and 0.50 equiv. (t=90 min). Analysis of the final reaction mixture after hydrolysis (Table 10, Method B) showed that a 91% yield for the Lewis acid assisted insertion (47% yield from the bromide) was obtained which consisted of the following compounds: *cis*-1-(1-methylethyl)-4-methylcyclohexane (74%), *trans*-1-(1-methylethyl)-4-methylcyclohexane (22%), and 5-ethyl-6-methyl-1-heptene (3%). No detectable amount of 4-(1-methylethyl)-1-methlyenecyclohexane was observed.

Ziegler-Natta Cyclization of 7-Bromo-6-methyl-1-heptene (203a). Bromide **203a** (381.8 mg, 2.0 mmol) was converted to alkyltitanocene **203b** in 97% yield following the general procedure. The product mixture prior to addition of the cocatalyst consisted of 6-methyl-1-heptene and *cis*- and *trans*-1,3-dimethylcyclohexanes (96:2:2), respectively (see Table 10, Method A). The titanium residue, after filtration and evaporation of solvents, was diluted with toluene (12 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added sequentially as follows: 1.0 equiv. (t=0 min), 0.75 equiv. (t=45 min), and 0.50 equiv. (t=90 min). Analysis of the final reaction mixture after hydrolysis (Table 10, Method B) showed that a 72% yield for the Lewis acid assisted insertion (63% yield from the bromide) was obtained which consisted of the following compounds: *trans* -1,3-dimethylcyclohexane (74%), *cis*-1,3-dimethylcyclohexane (17%), 3-methyl-1-methlyenecyclohexane (7%), and 6-methylhept-1-ene (2%).

Ziegler-Natta Cyclization of 7-Bromo-6-(1-methylethyl)-1-heptene (160a). Bromide **160a** (437.8 mg, 2.0 mmol) was converted to alkyltitanocene **160b** in 74% yield following the general procedure except that the transmetallation was performed in toluene. The product mixture prior to addition of the cocatalyst consisted of 6,7-dimethyl-1-octene and *cis*- and *trans*-1-(1-methylethy)-3-methylcyclohexanes (83:11:6), respectively (see Table 10, Method A). The

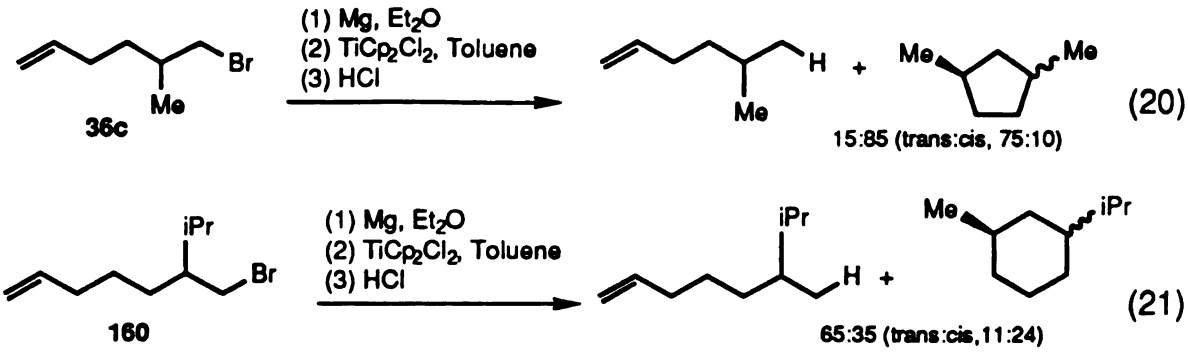
titanium residue after filtration and evaporation was diluted CH_2Cl_2 (30 mL), cooled to -78 °C, and 1.0 M $EtAlCl_2$ (2.25 eq) was added sequentially as follows: 1.0 equiv. (t=0 min), 0.50 equiv. (t=120 min), and 0.25 equiv. (t=240 min). Analysis of the final reaction mixture after hydrolysis (Table 10, Method B) showed that a 88% yield for the Lewis acid assisted insertion (63% yield from the bromide) was obtained which consisted of the following compounds: *trans*-1-(1-methylethy)-3-methylcyclohexane (70%), *cis*-1-(1-methylethy)-3-methylcyclohexane (18%), 3-(1-methylethyl)-1-methylenecyclohexane (9%), and 6,7-dimethyl-1-octene (2%).

CHAPTER 4.

MECHANISTIC STUDIES OF ZIEGLER-NATTA POLYMERIZATION: PROBING FOR α- OR β-HYDROGEN ACTIVATION

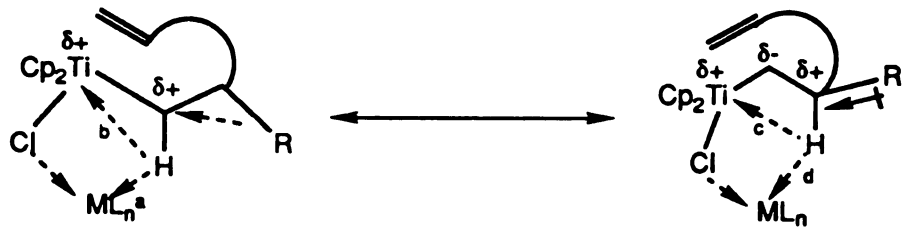
1. Introduction

During the development of our titanocene mediated ring-forming methodology, we observed peculiar behavior for both the 5-hexen-1-yl- and 6-hepten-1-yltitanocene chloride complexes when an alkyl group was in the β position with respect to the metal. For instance, reaction of a Grignard solution of **36c** in diethyl ether with titanocene dichloride resulted in nearly complete cyclization in less than one hour (eqn. 20). To fulfill our synthetic objectives at the time, we found that olefin insertion during transmetallation could be suppressed if the reaction was run in the presence of THF. This result was presumably due to the higher basicity of THF, which allowed for stronger complexation with MgX_2 in comparison to the corresponding diethyl ether complex. Substrates **36a-b** did not cyclize to any extent under these conditions. In an analogous situation, the MgX_2 salts catalyzed the cyclization of **160b** to an extent of 35%, even with THF present (eqn. 21). The most interesting aspect of this latter example was that these conditions promoted olefin insertion with an opposite stereochemical preference (cis:trans, 2:1) compared to that promoted with $EtAlCl_2$ (cis:trans, 8:92). These results have launched us into an exploration of the mechanism of Ziegler-Natta polymerization.



The apparent rate enhancement, observed only with an alkyl group present in the position β to the metal, suggested the possible intervention of an electronic effect. Possible explanations for these observations included either α- or β-hydrogen activation (Scheme 31).[74] During both α-hydrogen activation (**210**) and β-hydrogen activation (**211**), the cocatalyst presumably complexes the chloride atom on titanium, causing an increase in the positive charge on titanium and a simultaneous polarization, and thus weakening, of the carbon-titanium bond. Based on Figures 1-3 (see Introduction), there are precedents that either α- or β-hydrogens could interact with the metal center. The nature of this interaction is unclear, but assuming the interaction would be to stabilize the metal center, a partial negative charge on hydrogen would be necessary. Also, the possible interaction of the cocatalyst with either the α- or β-hydrogen cannot be ruled out. The net result would be the development of positive charge on either the α-carbon (**210**) or the β-carbon (**211**) depending on the mechanism. The role of the β-alkyl group could be to stabilize the development of the positive charge by either hyperconjugation (**210**) or through induction (**211**). Both α- or β-hydrogen activation could reasonably account for an increased rate of cyclization.

Scheme 31. Mechanistic Possibilities for Ziegler-Natta Polymerization: α- and β-Hydrogen Interactions

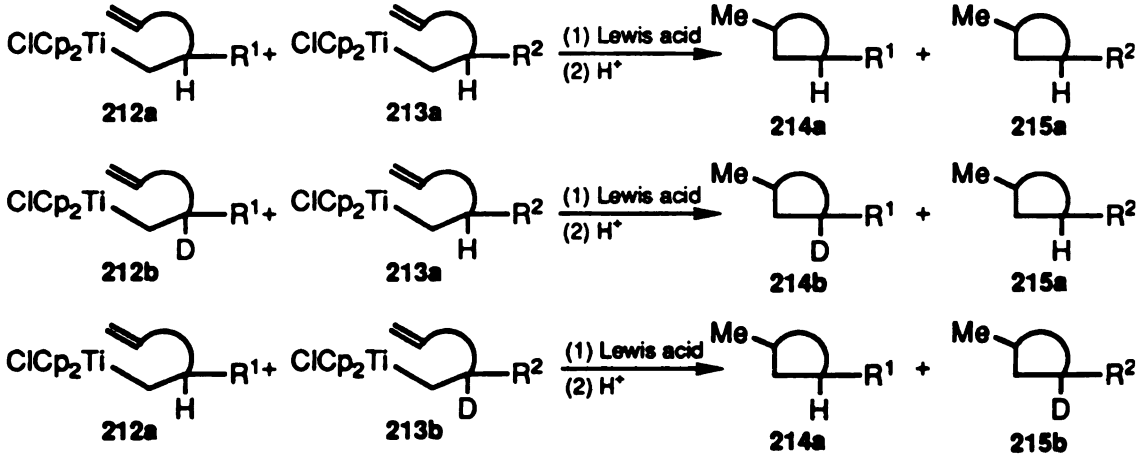


210 **211**

To test these potential pathways, we designed a series of competitive rate experiments (Scheme 32). Our idea resembled aspects of independent experiments reported by Grubbs[9a] and Bercaw,[9c] in which the relative strengths of carbon-hydrogen and carbon-deuterium bonds were central to the design. The major difference in our approach was how the deuterium isotope effect was to be measured. Both Grubbs and Bercaw used the stereochemistry of the cyclized products as an instrument for measuring an isotope effect. Our intentions were to compare the relative rates of olefin insertion of two similar alkenyltitanocene complexes in which one contained a hydrogen atom (α or β) and the other a corresponding deuterium atom (α or β). Ideally, the most informative reaction would be to directly monitor the relative rates of cyclization between **212a** and **213a** where $R^1=R^2$. However, we intended to monitor the cyclization progress using gas chromatographic techniques which would make this approach impossible. Alternatively, an indirect method for obtaining the same information is outlined in Scheme 32 in which $R^1\neq R^2$. First, cyclization of a mixture of **212a** and **213a** ($R^1\neq R^2$) will determine the minor role of the β-alkyl substituents on the relative rates of olefin insertion. By graphing the conversion versus time for each substrate, the relative rate of cyclization can be obtained from the ratio of the slopes [k_{rel}=slope(**212a**/**213a**)]. Secondly, **212b** and **213a** will be treated under the identical conditions and the resultant conversions graphed in a similar fashion.

In this way, k_H/k_D can be obtained by the following ratio: [slope(**212a/213a**)]/[slope(**212b/213a**)]. Finally, the competitive cyclization of **212a** and **213b** provides a control for the second cyclization. A similar series of competitive reactions will also be performed in which α,α-dihydrogen substrates will be compared to α,α-dideuteron substrates. These reactions outlined above could provide insight into the fundamental processes of Ziegler-Natta polymerization.

Scheme 32. Competitive Rate Experiments Designed to Test the Mechanistic Possibilities

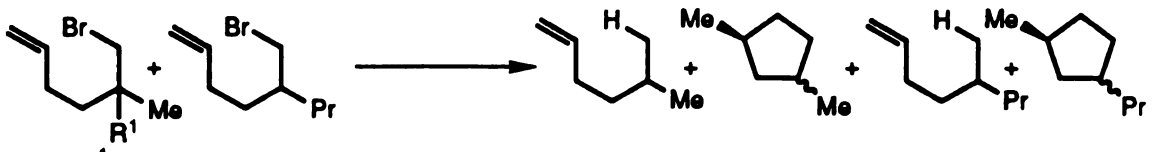


2. Preliminary Findings for the 2-Alkyl-5-hexen-1-yltitanocene Chlorides

Our initial investigation involved competitive rate experiments in which cyclization was to be facilitated under the transmetallation conditions (Scheme 33). Two major problems were associated with this system. First of all, quenching an aliquot of the Grignard intermediates revealed that 40% of the reaction mixture from **129** were cyclopentane products compared to 20% for **36c**. Secondly, transmetallation of these Grignard species to $TiCp_2Cl_2$ resulted in rapid (<20 minutes) cyclization upon warming to ambient temperature. When colder temperatures were maintained throughout the transmetallation process,

conversion did not occur to as great an extent. One major problem, SET cyclization during Grignard formation, could be avoided if THF was used as a solvent, but this also inhibited the effectiveness of MgX_2 as a Lewis acid and decreased the amount of cyclization. The problems associated with this system suggested that extraction of the pertinent rate information would be difficult. Specifically, the time window for monitoring the reaction progress was too small.

Scheme 33. Cyclization of 5-Hexen-1-yltitanocene Chlorides Performed Under the Transmetallation Conditions



36c : R^1=H	129	(1) Mg, Et_2O	80	20	62	38
		(2) $TiCp_2Cl_2$, Toluene -45 to 25 °C	25	75	13	87
125 : R^1=D	129	(1) Mg, Et_2O	80	20	62	38
		(2) $TiCp_2Cl_2$, Toluene -45 °C	80	20	62	38

In order to avoid the rapid and uncontrollable cyclization discussed above, we opted to pursue 7-bromo-1-heptene substrates. We have demonstrated that these substrates cyclized to a lesser extent during Grignard formation, and the corresponding titanocene derivatives underwent 6-*exo*-trig insertion more slowly than the corresponding 6-bromo-1-hexene compounds. Therefore, this modification has the potential for overcoming both of the problems associated with the cyclization of 6-bromo-1-hexene substrates, which should increase the window of observation with a simultaneous increase in the accuracy and precision of the data.

3. Optimization Studies for the Competitive Cyclization of 2-Alkyl-6-hepten-1-yltitanocene Chlorides with Me_2AlCl, MgX_2, and MAO

Our first task was to develop reproducible cyclization conditions using the aforementioned Lewis acids that would provide high yields of cyclic products, concurrent with a large window of time (90-180 minutes) to view the linear conversion to cyclic products. In order to graph conversion versus time and interpret the results with a high degree of certainty, we needed to accumulate enough data points (5-8) to minimize the error. These considerations are legitimate since an isotope effect in a similar system was reported to be $k_H/k_D=1.2$.[9c] The variables that were systematically changed include the Lewis acid, equivalents of Lewis acid, solvent, concentration, and temperature. We chose to investigate three Lewis acids for these competitive rate experiments, Me_2AlCl, MgX_2, and MAO. The interesting reversal in stereochemistry using MgX_2 as opposed to Me_2AlCl or $EtAlCl_2$, suggesting a different mechanism, coupled with the propensity of this catalyst to provide isotactic polypropylene made MgX_2 ideal for our investigation. Although the structure of this catalyst is unclear, MAO also furnished isotactic polypropylene which compelled us to study its behavior.

Table 11. Cyclization of Unpurified 175b Using MgX_2 or MAO

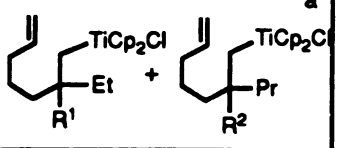
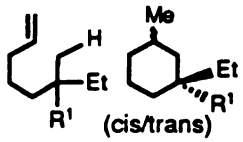
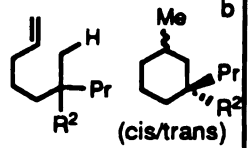
 [a]	time (min)		 (cis/trans)	 [b]	% Yield[c]
1) MgX_2 (X=Cl or Br, 1.0 equiv.), Toluene, 45 °C, Molarity = 0.02 M	0	96	3/1	0	
	420	41	39/8	4	d
2) $MgCl_2$ (8.0 equiv.) + MgX_2 (X=Cl or Br), Toluene, -45 to 25 °C, Molarity = 0.02 M,	0	96	3/1	0	
	210	44	24/20	5	93
	590	14	33/21	14	82
3) $MgCl_2$ (8.0 equiv.) + MgX_2 (X=Cl or Br), Toluene, -45 to 50 °C, Molarity = 0.02 M,	0	96	3/1	0	
	150	10	37/16	23	86
	410	10	27/15	24	76
4) MAO (2.0 equiv.), + MgX_2 (X=Cl or Br), Toluene, -45 to 25 °C, Molarity = 0.02 M,	0	96	3/1	0	
	80	46	25/24	5	100
	330	14	46/19	18	97

[a](1) **175a** , Mg, THF, 45 °C, (2) $TiCp_2Cl_2$, Toluene. [b]Numbers represent millimolar ratios scaled to 100 for time=0 and percentage for the final time. [c]Reference 69. [d]No internal standard was used in this reaction.

Our initial efforts for promoting the cyclization of **175b** saw a return to magnesium dihalides, either with the MgX_2 formed *in situ* during transmetallation or with an excess of the salts (Table 11). The alkyltitanocene chloride **175b** illustrated in Table 11 was prepared by the addition of a diethyl ether solution of the Grignard reagent to $TiCp_2Cl_2$ in toluene. After transmetallation was complete, the alkyltitanocene complex was not purified from the magnesium salts, but rather, the diethyl ether was removed *in vacuo* and the mixture diluted with CH_2Cl_2. Entry 1 illustrates the effect of one equivalent of MgX_2 on the cyclization process. After 4 hours at 25 °C, no cyclization was detected. However, heating this mixture to 45 °C led to 51% cyclization after 7 hours, at which time the reaction ceased. These conditions most notably produced a 5:1 ratio of

diastereomers selective for the cis isomer. In an attempt to increase the amount of conversion, excess $MgCl_2$ (8 equiv.) was employed at 25 °C (entry 2) and 50 °C (entry 3). As expected, higher temperatures facilitated conversion, yet product loss resulted after prolonged exposure to the reaction conditions. Interestingly, the use of excess MgX_2 caused a dramatic decrease in selectivity and also an increase in β-hydrogen elimination. Finally, entry 4 demonstrates the behavior of MAO (2 equiv.) in combination with MgX_2 (1 equiv.). The desirable features of this reaction were the high yield, near complete conversion, and the extended period of time required for conversion. Although these conditions appeared ideal for our study, the slow steady conversion proved difficult to repeat at this temperature. A limitation imposed by avoiding purification of the alkyltitanocene complexes before introduction of the cyclization catalyst was that occasionally the effect of concentrating the alkyltitanocene complexes in the presence of MgX_2 caused nearly complete cyclization. In order to alleviate this problem, all reactions henceforth were performed with a "magnesium free" alkyltitanocene solution, which was combined with a solution (or suspension in the case of $MgCl_2$ and $MgBr_2$) of the Lewis acid.

Table 12. Cyclization of Purified 168b and 175b Using MgX_2

a 	time (min)	b  (cis/trans)	 (cis/trans)	% Yield[c] Et/Pr
1) $MgCl_2$ (8.0 equiv.),	0	87 8/5	89 7/4	
1,2-DCE, 0 °C,	490	74 18/8	74 15/6	100/95
Molarity = 0.02 M				
R^1=H; R^2=H				
2) $MgCl_2$ (8.0 equiv.),	0	87 8/5	89 7/4	
1,2-DCE, 45 °C,	120	35 38/20	44 33/15	93/88
Molarity = 0.02 M,				
R^1=H; R^2=H				
3) $MgCl_2$ (8.0 equiv.),	0	94 4/2	95 3/2	
Toluene, 25 °C,	180	70 9/6	75 10/6	85/91
Molarity = 0.02 M,	255	52 16/10	54 16/10	78/80
R^1=H; R^2=H				
4) $MgCl_2$ (10.0 equiv.),	0	84 10/6	83 10/7	
Toluene:CH_2Cl_2 (3:1),	490	50 22/13	46 18/12	85/76
25 °C, Molarity = 0.02 M,				
R^1=H; R^2=H				
5) $MgCl_2$ (10.0 equiv.),	0	82 11/7	83 10/7	
Toluene:CH_2Cl_2:Et_2O	60	65 14/9	66 14/10	88/90
(2.5:1.0:0.5), 25 °C,	420	45 20/13	46 18/13	78/77
Molarity = 0.02 M,				
R^1=H; R^2=H				
6) $MgBr_2$ (2.0 equiv.),	0	92 5/3	92 5/3	
Toluene:Et_2O (>95:5),	420	62 13/9	60 14/10	84/84
25 °C, Molarity = 0.02 M,				
R^1=H; R^2=H				
7) $MgCl_2$ (2.0 equiv.),	0	92 5/3	92 5/3	
$MgBr_2$ (2.0 equiv.),	90	78 11/6	75 9/6	95/90
Toluene:CH_2Cl_2	230	46 22/20	51 16/14	88/81
(2.5:1.0), 25 °C,	350	22 27/29	31 23/14	78/68
Molarity = 0.02 M,				
R^1=H; R^2=H				

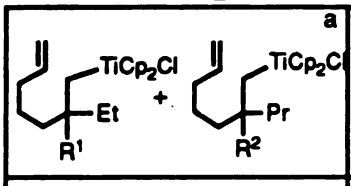
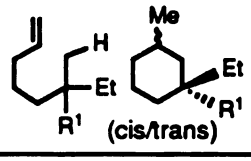
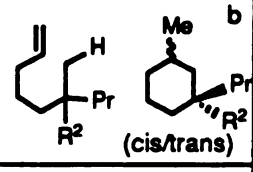
[a](1) 168a and175a , Mg, THF, 45 °C, (2)$TiCp_2Cl_2$,Toluene. [b]Numbers represent millimolar ratios scaled to 100 for time=0 and percentage for the final time. [c]Reference 69.

Using the "magnesium free" alkyltitanocene solution, we were persistent in our quest to optimize MgX_2 promoted cyclizations. The solvent 1,2-dichloroethane has been shown to be an effective solvent for olefin polymerization. Entries 1 and 2 (Table 12) illustrate the combined effects of $MgCl_2$ (8 equiv.) in 1,2-dichloroethane at either 0 °C or 45 °C. Although no cyclization was observed at 0 °C, promising results were achieved at higher temperatures, yet the reaction ceased after two hours. Entries 3-7 represented systematic variations in the reaction conditions in an attempt to reproduce the results obtained in Table 11, in which the organometallic complex was not isolated. During those particular cyclizations, toluene and CH_2Cl_2 were present, however, the exact amount of diethyl ether and the precise composition of MgX_2 (X=Br or Cl) was not clear. Cyclization of the mixture of alkyltitanocene complexes with $MgCl_2$ (8 equiv.) in toluene (entry 3) or in a toluene:CH_2Cl_2 mixture (3:1, entry 4) produced the same overall conversion and comparable yields. Since $MgCl_2$ was virtually insoluble in the previous solvent systems, the need for a small amount of diethyl ether seemed necessary to solubilize the catalyst. To explore this avenue, entries 5 and 6 utilized varying amounts of diethyl ether but, to our dismay, no significant improvements were observed. Slightly improved conversion was finally realized when a 1:1 mixture of $MgCl_2$:$MgBr_2$ (entry 7) was used. However, the irreproducibility of the MgX_2 catalysis prompted us to pursue the other Lewis acids.

We have found in previous investigations that Me_2AlCl was an efficient catalyst for cyclohexane formation. During the optimization of **164b**, we observed a linear conversion to **197** when Me_2AlCl (1.0 equiv.) in toluene (0.01 M) was reacted with **164b** at -35 °C. Since these conditions appeared to provide results that fulfilled our initial criteria, we treated a mixture of the β-ethyl- and β-propyl-titanocene complexes under these conditions (Table 13). In entry 1, a slight

variation in the previous conditions were used which resulted in complete cyclization in under 30 minutes. Using the precise conditions as in **164b**, only a marginal improvement in time was realized. We determined that accurate analysis of the reaction progress under more dilute conditions (<0.01 M) was not reliable. Although an extensive study of lesser equivalents of Me_2AlCl was not completed, we decided to concentrate all efforts on MAO.

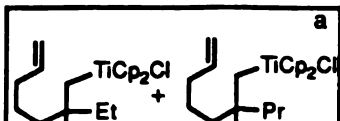
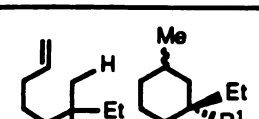
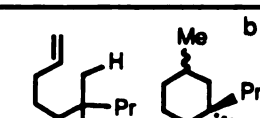
Table 13. Cyclization of Alkyltitanocene Chlorides Promoted with Me_2AlCl

 [a]	time (min)	 (cis/trans)	 [b] (cis/trans)	% Yield[c] Et/Pr
1) Me_2AlCl (1.5 equiv.), Touene, -50 to -35 °C, Molarity = 0.015 M R^1=H; R^2=D	0	83 11/6	83 11/6	
	30	8 28/58	7 29/55	94/91
2) Me_2AlCl (1.0 equiv.), Toluene, -50 to -35 °C, Molarity = 0.01 M, R^1=H; R^2=H	0	75 18/7	83 10/7	
	20	35 21/35	52 19/29	91/100
	55	7 28/53	12 32/56	88/100

[a] (1)168a and 178a or 168a and175a , Mg, THF, 45 °C, (2)$TiCp_2Cl_2$, Toluene. [b] Numbers represent millimolar ratios scaled to 100 for time=0 and percentage for the final time. [c] Reference 69.

Tables 14 and 15 represent preliminary results using MAO. The information contained in these tables was separated based on the order of addition of the reagents, and the form (solid or solution) in which MAO was handled. In Table 14, MAO was weighed under an inert atmosphere prior to each reaction, diluted with toluene and cooled to -78 °C, followed by addition of a solution of the alkyltitanocene complexes. In contrast, the results in Table 15 were obtained by the addition of a 0.5 M solution of MAO (in toluene) to a -78 °C solution of the alkyltitanocene complexes. In general, the latter approach was more reliable since the precise amount of catalyst was more easily measured (in the former case, 10-15 mg of MAO were required for each reaction).

Table 14. Cyclization of Alkyltitanocene Chlorides Promoted with MAO

a 	time (min)	b  (cis/trans)	 (cis/trans)	% Yield[c] Et/Pr
1) MAO (1.5 equiv.),	0	79	12/9	79	12/9	
CH_2Cl_2, -78 to 25 °C, 25 °C	360	70	12/9	79	12/9	91/100
Molarity = 0.035 M	660	36	27/18	40	29/16	81/85
R^1=D; R^2=H						
2) MAO (1.5 equiv.),	0	88	8/4	88	7/5	
Toluene, -78 to 25 °C,	100	11	28/50	15	27/45	89/87
Molarity = 0.01 M,						
R^1=H; R^2=H						
3) MAO (0.75 equiv.),	0	94	4/2	95	3/2	
Toluene, -78 to 25 °C,	25	5	26/64	7	25/59	95/91
Molarity = 0.02 M,						
R^1=H; R^2=H						
4) MAO (3.0 equiv.),	0	83	11/6	83	11/6	
CH_2Cl_2, -78 to -55 °C,	65	6	28/54	7	29/51	88/87
Molarity = 0.02 M,						
R^1=H; R^2=D						

[a](1) 168a and175a or 168a and178a or 171a and175a , Mg, THF, 45 °C, (2)$TiCp_2Cl_2$, Toluene. [b]Numbers represent millimolar ratios scaled to 100 for time=0 and percentage for the final time. [c]Reference 69.

Although the experimental technique used to obtain the results in Table 14 was suspect, qualitative information about the necessary catalyst concentration and reaction temperature was available. In entry 1, no cyclization was observed at -78 °C after 6 hours with MAO (1.5 equiv.). However, allowing the reaction mixture to warm to ambient temperature overnight resulted in approximately 50% conversion. More importantly, these conditions showed a preference for the cis isomer (2:1) which paralleled the results for MgX_2. If the reagents were added in the same manner as entry 1, but warmed to ambient temperature immediately (entries 2 and 3), cyclization was very rapid and the product mixture was trans selective (2:1). Entry 4 showed that with higher MAO concentrations (3 equiv.), cyclization could be promoted at -55 °C, and trans selectivity (64:36) was again

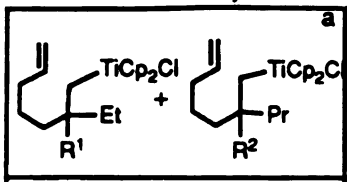
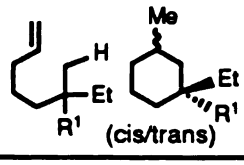
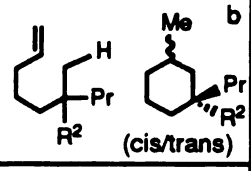
observed. The observed selectivity dependence on the temperature is not without precedent. Erker has recently reported that the tacticity of propylene polymerization was drastically reversed at different temperatures with MAO (isotactic at -50 °C and syndiotactic at -10 °C).[75] Apparently, based on the stereochemical outcome for entries 2 and 3, cyclization must have been complete before ambient temperature was reached. The stereochemical results in entry 1 have not been duplicated. During the initial six hours of sampling the reaction, a large portion of the catalyst was probably hydrolyzed, which prevented significant cyclization from occurring prior to ambient temperature being reached. Exhaustive attempts to reproduce these results have utilized less MAO, more dilute conditions, inverse addition of reagents, and mixing of reagents at ambient temperatures. All of these attempts have been met without reward.

Addition of a stock solution of MAO to the alkyltitanocene complexes provided only minor improvements for controlling the cyclization rate and the reproducibility of any set of reaction conditions (Tables 15-17). The results in Tables 15-17 demonstrated the necessary ratio of alkyltitanocene complexes:MAO to be between 1.0:0.5 to 1.0:0.65. However, comparison of the results in entries 2 and 3 (Table 15), and entries 4 and 5 (Table 15), demonstrated that under identical conditions, a marked difference in cyclization rate (or no cyclization at all, entry 3) was observed. These divergent results could be attributed to the age of the alkyltitanocene complexes or to the technique with which MAO was added. An apparent trend was that 12-24 hours after the alkyltitanocene complexes were purified, a slight increase in the MAO concentration was needed to initiate cyclization. This suggests that adventitious moisture or oxygen may play a role in retarding cyclization. Another possible scenario for the divergent results was that the requisite amount of MAO needed for cyclization never reached the solution. In order to suppress rapid cyclization,

MAO solution was precooled by slow addition down the side of the flask (approximately 0.25-0.50 inches above the solution) to a -78 °C solution of the alkyltitanocene complexes, and rinsed by vigorous stirring. What may have been occuring was that MAO was crystallizing on the side of the flask and failed to redissolve.

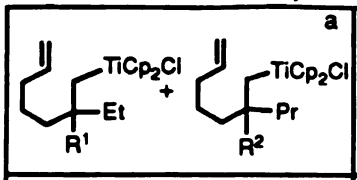
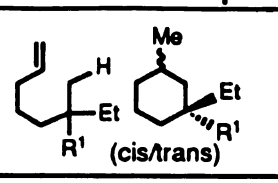
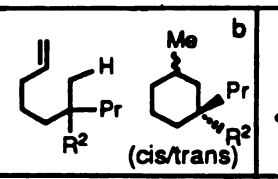
Another level of frustration encountered during this study was an uncontrollable, exponential conversion to cyclic products in the initial minutes after MAO was added (see select entries in Tables 16 and 17). Moreover, during the initial exponential rise, the substrate with the β-ethyl group with respect to titanium cyclized to a far greater exent than the β-propyl substrate. Although we can merely speculate as to the cause of the difference in rate in the initial time period, we can say that these results were not isotope dependent. The net effect was to diminish the useful window of observation.

Table 15. Competitive Cyclization of β-Hydrogen vs β-Hydrogen (168b vs 175b) Promoted Under the Optimized Conditions for MAO

 [a]	time (min)	 (cis/trans)		 [b] (cis/trans)		% Yield[c] Et/Pr
1) MAO (0.5 equiv.),	0	97	2/1	96	2/2	
Toluene, -78 to 25 °C,	20	<1	33/64	9	31/58	100/97
Molarity = 0.02 M						
R^1=H; R^2=H						
2) MAO (0.5 equiv.),	0	91	6/3	90	6/4	
Toluene, -78 to -50 °C,	30	80	11/9	84	9/7	100/100
Molarity = 0.02 M,	150	55	19/26	67	13/18	100/100
R^1=H; R^2=H	420	21	29/50	48	20/32	100/100
3) MAO (0.5 + 0.25 equiv.),	0	95	3/2	95	3/2	
Toluene, -78 to -50 °C,	55	87	9/4	91	4/3	100/98
Molarity = 0.02 M,	130					
R^1=H; R^2=H 0.25eq	230	<1	33/64	4	29/59	98/92
4) MAO (0.65 equiv.),	0	91	6/3	93	4/3	
Toluene, -78 to -50 °C,	120	43	19/34	59	15/23	96/97
Molarity = 0.02 M,	240	5	32/56	25	24/44	93/93
R^1=H; R^2=H	300	3	32/62	21	26/50	97/97
5) MAO (0.65 equiv.),	0	91	6/3	90	6/4	
Toluene, -78 to -50 °C,	60	?	?	48	20/32	100/100
Molarity = 0.02 M,	120	<1	31/69	7	28/64	100/99
R^1=H; R^2=H						

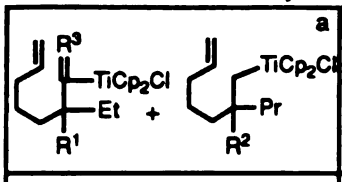
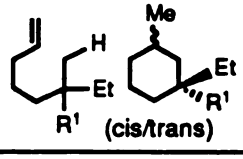
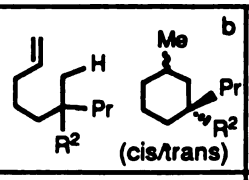
[a] (1) 168a and175a , Mg, THF, 45 °C, (2)$TiCp_2Cl_2$, Toluene. [b] Numbers represent millimolar ratios scaled to 100 for time=0 and percentage for the final time. [c]Reference 69.

Table 16. Competitve Cyclization of β-Hydrogen vs β-Deuteron (168b vs 178b) Promoted Under the Optimized Conditions for MAO

 a	time (min)	 (cis/trans)		 b (cis/trans)		% Yield[c] Et/Pr
1) MAO (0.65 equiv.),	0	96	3/1	96	3/1	
Toluene, -78 to -45 °C,	30	23	26/51	45	20/35	100/100
Molarity = 0.02 M	120	<1	33/66	28	24/48	100/100
R^1=H; R^2=D						
2) MAO (0.55 equiv.),	0	95	3/2	94	4/2	
Toluene, -78 to -50 °C,	10	54	19/27	70	12/18	100/100
Molarity = 0.02 M,	25	40	21/39	59	15/26	100/100
R^1=H; R^2=D	40	23	26/51	48	19/33	100/100
	60	13	28/57	23	29/45	98/97
3) MAO (0.50 equiv.),	0	93	4/3	93	4/3	
Toluene, -78 to -55 °C,	10	61	15/23	70	12/18	99/100
Molarity = 0.02 M,	40	25	25/49	45	20/35	99/100
R^1=H; R^2=D	90	10	29/60	21	27/51	99/99
4) MAO (0.4 equiv.),	0	93	4/3	93	4/3	
Toluene, -78 to 25 °C,	10	84	8/8	84	8/8	100/100
Molarity = 0.02 M, 25 °C	105	53	25/22	80	10/10	100/100
R^1=H; R^2=D	145	4	38/58	19	31/47	100/97

[a](1) 168a and178a , Mg, THF, 45 °C, (2)$TiCp_2Cl_2$, Toluene. [b]Numbers represent millimolar ratios scaled to 100 fo time=0 and percentage for the final time. [c]Reference 69.

Table 17. Competitive Cyclization of β-Deuteron vs β-Hydrogen (171b vs 175b) and β,β-Dideuteron vs α,α-Dihydrogen (184b vs 175b) Promoted Under the Optimized Conditions for MAO

 a	time (min)	 (cis/trans)	 b (cis/trans)	% Yield[c] Et/Pr
1) MAO (0.50 + 0.05 equiv.),	0	97	2/1	97	2/1	
Toluene, -78 to -55 °C,	20	81	8/11	85	6/9	100/100
Molarity = 0.02 M	95	73	10/17	80	7/13	100/100
R^1=D; R^2=H; R^3=H, H	120	64	13/22	75	8/16	99/98
0.05 equiv.	140	47	20/38	49	17/32	99/98
	180	4	30/65	9	30/61	99/100
2) MAO (0.55 equiv.),	0	92	5/3	90	6/4	
Toluene, -78 to -55 °C,	10	45	22/33	60	16/24	100/100
Molarity = 0.02 M,	25	30	26/43	47	20/32	99/99
R^1=H; R^2=H; R^3=D, D	55	21	28/49	35	23/40	98/98
	70	13	29/55	20	27/50	97/97
3) MAO (0.55 equiv.),	0	d	7/6	92	5/3	
Toluene, -78 to -55 °C,	10	d	16/21	62	13/20	d/95
Molarity = 0.02 M,	25	d	23/31	60	14/22	d/96
R^1=H; R^2=H;R^3=D, D	55	d	23/44	37	21/38	d/96

[a](1) 171a and175a or 184a and175a , Mg, THF, 45 °C, (2)$TiCp_2Cl_2$, Toluene. [b]Numbers represent millimolar ratios scaled to 100 for time=0 and percentage for the final time. [c]Reference 69. [d]Could not be determined accurately due to poor baseline resolution in that portion of the gas chromatographic trace.

Figures 4-7 illustrate a graphic view of the relative rate data for various competitive experiments. If the initial growth period is ignored and only the linear portion considered for each graph, the α- or β- deuterium atoms had no measurable effect on the rate. However, with the minimum number of data points obtained in each linear portion of the graph, the error in these slopes was considerable. In spite of these shortcomings, an amazing correlation was observed. For the competitive cyclization of **168b** and **175b** (Figure 4), a relative rate of $k_{168b}/k_{175b}=1.22$ was determined, which demonstrated the contribution of the alkyl group to the rate of insertion. Figure 5 suggests that β-hydrogen activation does not enter into the mechanism under the conditions that employ MAO, as the relative rate was comparable to Figure 4, $k_{168b}/k_{178b}=1.24$. The best graph of the relative rate data for the control experiment, Figure 6, was not conclusive, as the erroneous graph indicates. Finally, the test for α-hydrogen activation is illustrated in Figure 7 and the relative rate calculated to be $k_{184b}/k_{175b}=1.30$. These results indicate that α-hydrogen activation is likewise, not important to the mechanism for this system.

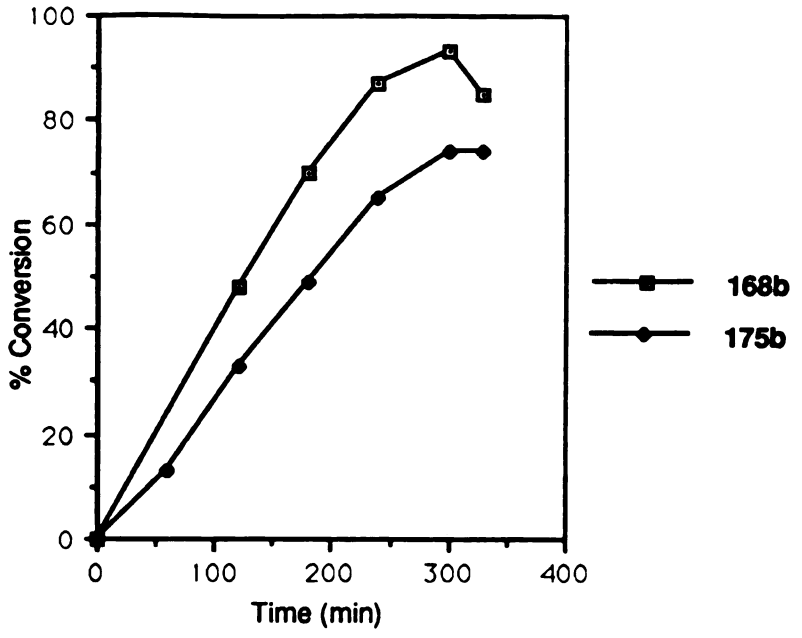


Figure 4. Competitive Cyclization Between **168b** and **175b** (see Table 15, entry 4). Slopes were calculated using a simple line program and omitting the exponential portions of the graph. The relative rate was calculated to be: $k_{rel}=k_{168b/k175b}=1.22$.

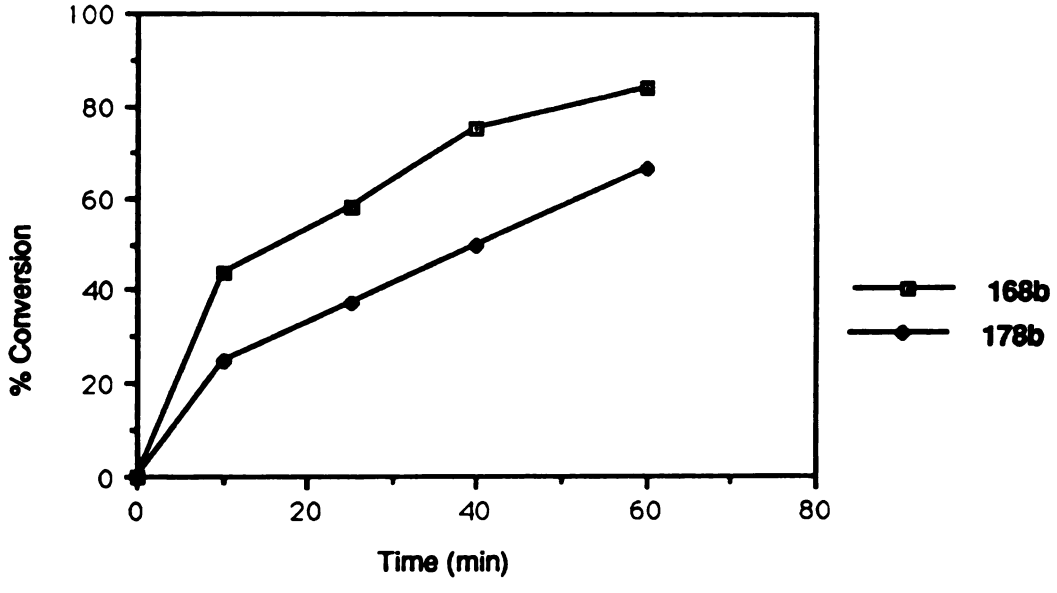


Figure 5. Competitive Cyclization Between **168b** and **178b** (see Table 16, entry 2). Slopes were calculated using a simple line program and omitting the exponential portions of the graph. The relative rate was calculated to be: $k_{rel}=k_{168b/k178b}=1.24$.

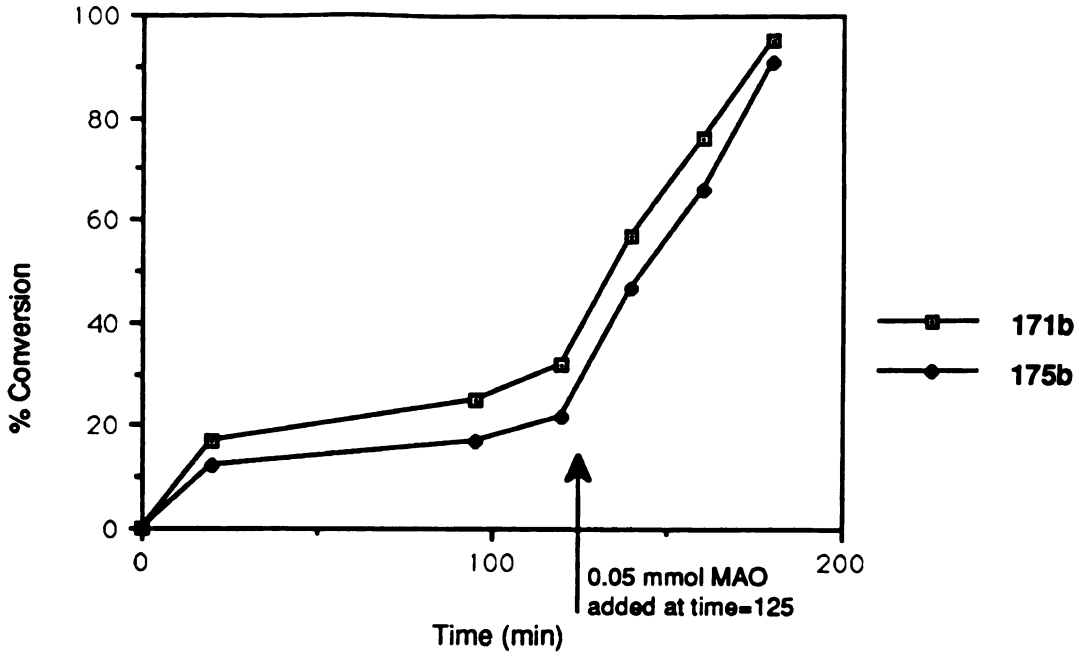


Figure 6. Competitive Cyclization Between **171b** and **175b** (see Table 17, entry 1). Slopes were calculated using a simple line program and omitting the exponential portions of the graph. Relative rate calculated to be: $k_{rel}=k_{171b}/k_{175b}=1.60$.

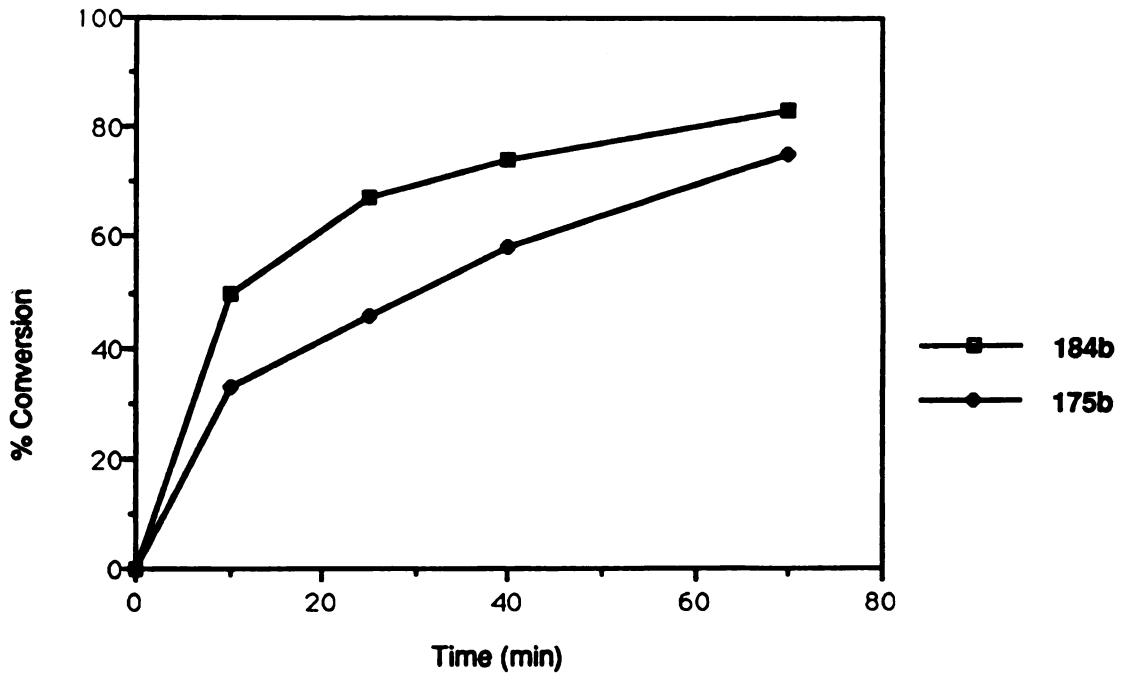


Figure 7. Competitive Cyclization Between **184b** and **175b** (see Table 17, entry 2). Slopes were calculated using a simple line program and omitting the exponential portions of the graph. The relative rate was calculated to be: $k_{rel}=k_{184b}/k_{175b}=1.30$.

Athough the above results suggest that α- and β-hydrogen activation do not participate in the mechanism, the limited data points for each graph do not provide confidence for any firm conclusion. In order to more accurately assess the situation, we have recently prepared 6-butyl-7-bromo-1-heptene (**182**) and plan to compare it to **175**. Preliminary results demonstrated that **182b** underwent cyclization more slowly than the β-propyl substrate (**175b**) in the initial time after MAO was added. A trend has been clearly established in which the longer β-alkyl chains gave rise to decreased cyclization in the early stages of the reaction. This new substrate should allow for the rapid completion of this study.

4. Conclusion

Although these results were not conclusive as to the existence of α- or β-hydrogen activation, conditions have been worked out using MAO that should allow this project to be completed soon. Although, preliminary results discussed here indicate that olefin insertion promoted by MAO did not show an α- or β-hydrogen effect. A number of interesting stereochemical observations were made based on the Lewis acid and the temperature of the reaction. It was shown that both MAO and MgX_2 were selective for the cis isomer when cyclization was carried out at 25 °C or higher. Yet, when lower temperatures were employed with MAO, the trans isomer was preferentially obtained. The future of this mechanistic project will be directed towards the investigation of the magnesium catalysts in an attempt to understand the nature of stereochemistry obtained. For now, the secrets of Ziegler-Natta polymerization are still secure.

5. Experimental

Methaluminoxane (MAO). A Schlenk flask was loaded with $Al_2(SO_4)_3(H_2O)_{(14-18)}$ followed by the removal of oxygen under vacuum and purging with argon. The aluminum sulfate was suspended in toluene (80 mL) and the flask immersed in a 25 °C water bath. Me_3Al (20 mL, 209 mmol) was diluted with toluene (20 mL) and the solution was added rapidly, *via* cannula, under argon pressure to the aluminum sulfate suspension, after which the reaction mixture was heated to 40 °C for 15-20 hours. The MAO was purified by filtration under argon using a Schenk filter. To accomplish this purification, the slurry was transferred to the filter *via* cannula. The solvent was removed *in vacuo* and the MAO was stored under nitrogen. For the reactions in Table 14, MAO (MW=130 g/mol) was weighed under nitrogen prior to each reaction, and diluted with the appropriate solvent. For the all other reactions employing MAO, a 0.5 M MAO solution (toluene) was used (3.25 g MAO, 25 mmol, 50 mL toluene).

Magnesium Dibromide. Magnesium turnings (1.46 g, 60 mmol) were loaded in a 3-necked flask equipped with a reflux condenser and a dropping funnel, and diethyl ether (30 mL) was added. An diethyl ether solution of 1,2-dibromoethane (11.27 g, 60 mmol, 10 mL diethyl ether) was added slowly to the magnesium metal over 2 hours followed by heating to reflux for an additional 2 hours. Diethyl ether was removed under reduced pressure and the white precipitate was heated 150 °C under vacuum (<0.001 mm Hg) for 8-10 hours. The white solid was stored under nitrogen.

General Procedure for Metal Mediated Cyclizations Using Unpurified Alkyltitanocene Chlorides. A Schlenk flask was charged with magnesium (583 mg, 24 mmol), flame dried under vacuum (<0.001 mm Hg), purged with argon

prior to the addition of diethyl ether (4 mL). Alkyl bromide **175** (438 mg, 2 mmol) was slowly added to the magnesium over 6 hours using a gas tight syringe. After the addition was complete, the reaction mixture was allowed to stir for an additional 4 hours. In a separate flask was loaded $TiCp_2Cl_2$ (548 mg, 2.2 mmol), and the flask was subsequently evacuated under reduced pressure, and purged with argon. The $TiCp_2Cl_2$ was suspended in toluene (8 mL) and the flask cooled to -50 °C. The alkylmagnesium bromide was transferred to the $TiCp_2Cl_2$ suspension *via* cannula and rinsed with additional diethyl ether (1 mL). The reaction temperature was maintained at -50 °C for 30 minutes and then warmed to ambient temperature for an additional 5 hours.

(A) Magnesium Dihalide Promoted Cyclization Using *in situ* MgX_2. After transmetallation was complete, the reaction mixture was brought to 45 °C (Table 11; entry 1). Cyclization was promoted using the MgX_2 (X= Cl or Br) which was formed *in situ* by the reaction of the Grignard reagent and $TiCp_2Cl_2$.

(B) Magnesium Dihalide Promoted Cyclization Using Excess MgX_2 or MAO. After transmetallation was complete, the diethyl ether was removed under vacuum and the reaction mixture was diluted with CH_2Cl_2 (5 mL). In a separate flask was loaded either $MgCl_2$ (189 mg, 1.98 mmol, Table 11; entries 2 and 3) or MAO (86 mg, 0.66 mmol, Table 11; entry 4) under and atmosphere of nitrogen and diluted with toluene (8 mL). A solution of **175b** (2.0 mL, 0.33 mmol) was added to a -45 °C solution (or suspension) of the respective Lewis acids, *via* syringe, and that temperature maintained for 10 minutes followed by warming to the desired temperature (see Table 11).

General Procedure for Metal Promoted Cyclizations Using Purified (MgX_2 Free Solutions) Alkyltitanocene Chlorides. A Schlenk flask was charged with magnesium (780 mg, 32 mmol), flame dried under vacuum, and purged with argon. THF (4 mL) was added to the flask and heated to 45 °C. In a

typical competitive rate experiment, a mixture of alkyl bromides (1 mmol each) was simultaneously added to the magnesium over 6 hours using a gas tight syringe and after the addition was complete, the reaction temperature was maintained for an additional 4 hours. In a separate Schlenk flask was loaded $TiCp_2Cl_2$ (548 mg, 2.2 mmol) and the flask was evacuated and purged with argon. The $TiCp_2Cl_2$ was suspended in toluene (8 mL) and cooled to -78 °C. The Grignard reagents were transferred *via* cannula under argon pressure to the cold suspension of $TiCp_2Cl_2$ and rinsed with additional THF (2 mL). The transmetallation reaction was maintained at -78 °C for 8 hours and then allowed to warm to ambient temperature for an additional 90 minutes, at which time the reaction mixture was diluted with hexane (25 mL) and cooled to 0 °C. The combined action of the hexane and cold temperatures caused most of the MgX_2 and excess $TiCp_2Cl_2$ salts to fall out of solution. The cold reaction mixture was transferred *via* cannula under argon pressure to a Schlenk filter and sequentially washed with cold hexane (3 x 7 mL). The alkyltitanocene chlorides were evaporated to dryness under vacuum (<0.001 mm Hg) to leave behind a dark red oil (or slurry). Toluene (30 mL) and an internal standard were added to the alkyltitanocene chlorides and the concentration of each substrate determined by gas chromatographic techniques. All subsequent reactions utilized this stock solution of known molarity.

(A) Competitive Rate Cyclizations Promoted by MgX_2 or Crystalline MAO. $MgCl_2$, $MgBr_2$ (or both, see Table 12; entry 3) or MAO were loaded in a Schlenk flask under nitrogen, suspended or dissolved in the solvent employed, and cooled to low temperature (see Table 12 and 13 for more details on each reaction). A calculated volume of the alkyltitanocene chlorides was added over one minute to the Lewis acid, maintained at that temperature for 10 minutes, and finally warmed to the appropriate temperature.

(B) Competitive Rate Cyclizations Promoted by Me_2AlCl or MAO. Solutions of Me_2AlCl and MAO were prepared by dissolving the Lewis acids in an appropriate volume of toluene to prepare a 0.5 M solution of each. A calculated volume of the alkyltitanocene chloride solution was diluted to the appropriate concentration (see Table 14, 15, 16, or 17) and cooled to either -50 °C if Me_2AlCl was to be used, or -78 °C if MAO was to be used. The appropriate Lewis acid was taken up in a gas tight syringe and slowly added down the side of the flask about 0.5 inches above the solution, and the flask was vigourously swirled to rinse the sides of the flask. The initial temperature employed was maintained for 10 minutes and then warmed to the described temperature (see Table 14, 15, 16, or 17 for more details).

CONCLUSION

The development of a novel ring-forming method which featured an intramolecular monomeric analog of Ziegler-Natta polymerization was discussed. The ease with which unactivated olefins reacted with the carbon-titanium bond was demonstrated. The metal and its surrounding ligands played a significant role during the carbocyclization, controlling both the regio- and the stereochemistry of bond formation for both 5-hexen-1-yl- and 6-hepten-1-yltitanocene chlorides. *Exo* insertion was the sole pathway observed in both cases. When an alkyl group was located on the alkyl tether, excellent and predictable diastereomeric excesses were achieved during carbon-carbon bond formation, in most cases. This ring-forming method represents the first procedure that did not result in a loss of selectivity or efficiency when extended to six-membered ring synthesis. This general and versatile procedure will certainly enhance the repertoire of carbon-carbon bond forming reactions available to the synthetic chemist.

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