NEW SYNTHETIC METHODOLOGIES UTILIZING REDUCTIVE CYCLIZATIONS CATALYZED OR MEDIATED BY TITANOCENE COMPLEXES

by

Natasha M. Kablaoui

A.B. Chemistry, Princeton University, 1992

Submitted to the Department of
Chemistry in Partial Fulfillment of the
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Massachusetts Institute of Technology

June 1997

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ABSTRACT

A new titanocene-catalyzed cycloreduction of enones to cyclopentanols, which proceeds through a metallacyclic intermediate, is described. The key step in the process is the cleavage of the titanium-oxygen bond in the metallacycle by a silane to regenerate the catalyst. Mechanistic aspects of the reaction are discussed and the diastereoselectivity of the transformation is studied using both achiral and chiral substrates. An *in situ* protocol for the generation of the air- and moisture-sensitive catalyst is also discussed.

A novel route to γ-butyrolactones is presented in which enones are converted to lactones with complete diastereoselectivity using a titanocene reagent. This heteroatom-containing varient of the Pauson-Khand reaction proceeds through the carbonylation of an oxatitanocycle followed by reductive elimination to produce the γ-butyrolactones. An example of the tranformation of an ynone to a fused butenolide using this methodology is also presented.

A method for the tranformation of *o*-allyl-aryl-ketones to γ-butyrolactones using a catalytic amount of either $Cp_2Ti(PMe_3)_2$ or $Cp_2Ti(CO)_2$ is described. The mechanism is similar to that for the stoichiometric conversion of enones to γ-butyrolactones, except that titnocene dicarbonyl is reactive towards *o*-allyl-aryl-ketones. We have investigated the scope and limitations of this catalytic methodolgy. Our mechanistic studies are consistent with the view that the key step in this catalytic cycle is the formation of a charge transfer complex or involves reversible electron transfer between the catalyst and the substrate. We have also found that we can carry out the transformation using the chiral (ethylene-bis-tetrahydroindenyl)titanium dimethyl complex [(*R*,*R*)-(EBTHI)$TiMe_2$] to afford products with varying degrees of enantiomeric excess.

Thesis Supervisor: Professor Stephen L. Buchwald

Title: Camille and Henry Dreyfus Professor of Chemistry

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During the course of my graduate work, there have been so many people involved both in my development as a scientist and in keeping me sane that I'm sure that I cannot fit everyone on this page. I would like to make special mention of a few of those people.

As for people in the lab, I'd like to first thank my advisor, Steve Buchwald, for his support and guidance over the years. I truly appreciate the myriad opportunities that he presented to me, and even though they were sometimes painful (the grant) I realize how valuable those experiences will be during my entire career. Special thanks also goes to Fred Hicks, who has been my collaborator on much of the work presented in this thesis. Our discussions about science and whatever else might have come up have been extremely valuable; plus he amuses me. Dr. Rick Broene was my baymate for the first 7 months in the lab, and even though nothing ever worked until after he left, I thank him for his help and encouragement even from afar. Finally, my classmates Andy Peat and Mr. Matt Reding have been my cohorts from Tang to graduation, and I have certainly appreciated their camaraderie along the way.

I also have to thank "the girls." The women in the Buchwald group (and of course the honorary girls) have been very supportive and fun, and I especially enjoyed our periodic "girl day" celebrations. Cheers to Linda Molnar, Malisa Troutman, Mary Beth Carter, Seble Wagaw, Nancy Lee (Mom), Shelley Bower, Nora Radu, Tricia Breen, Shana Sturla, and Jaesook Yun. Thanks also go to the women who helped to coordinate the Women in Chemistry conference and the Women in Chemistry lunches.

Graduate school can often be a stressful place, and without a few distractions outside the lab I think I may have snapped. I especially would like to thank Jennifer Joy G and everyone associated with her for being such a terrific group and for providing an outlet for stress and any unsightly aggression. I have derived strength and sanity from this group as well as some wonderful friends.

I also would like to thank my family. My parents have been extremely supportive (and very forgiving) during my time in graduate school. I especially owe them thanks for always encouraging my interest in science and math — I have come to realize that many girls do not have that luxury when they are growing up. Finally there was this guy that I met the very first day of graduate school — I think we went out to dinner. The friendship and support of my soon-to-be husband Alex Brodsky have been integral to my survival in the lab and to my happiness outside the lab.

PREFACE

Parts of this thesis have been adapted from the following articles co-written by the author:

Kablaoui, N. M.; Buchwald, S. L. "Reductive Cyclization of Enones by a Titanium Catalyst" *J. Am. Chem. Soc.* **1995**, *117*, 6785.

Kablaoui, N. M.; Buchwald, S. L. "Development of a Method for the Reductive Cyclization of Enones by a Titanium Catalyst" *J. Am . Chem. Soc.* **1996**, *118*, 3182.

Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. "A Diastereoselective Synthesis of γ-Butyrolactones from Enones Mediated or Catalyzed by a Titanocene Complex" *J. Am. Chem. Soc.* **1996**, *118*, 5818.

Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. "Titanocene-Catalyzed Cyclocarbonylation of *o*-Allyl Aryl Ketones to γ-Butyrolactones" *J. Am. Chem. Soc.*, **1997**, *119*, 4424.

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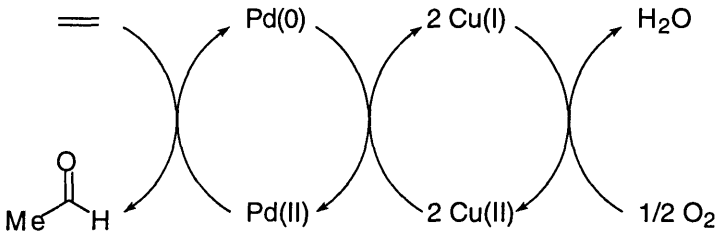
Introduction

Recently there has been an explosion of interest in the development of transition metal-mediated and -catalyzed processes for use in organic chemistry. Transition metals can provide novel patterns of reactivity that are inaccessible using traditional methods of organic chemistry, thus allowing for more direct and elegant routes to complex organic products. A serious drawback, however, to the use of transition metals in organic chemistry is the experimental difficulty in applying the procedures which often involve the manipulation of air- and moisture-sensitive materials as well as the use of stoichiometric amounts of expensive and toxic metals. Therefore, one of the most active areas of investigation in the field of organometallic chemistry has been in the use of transition metals as catalysis for organic reactions.

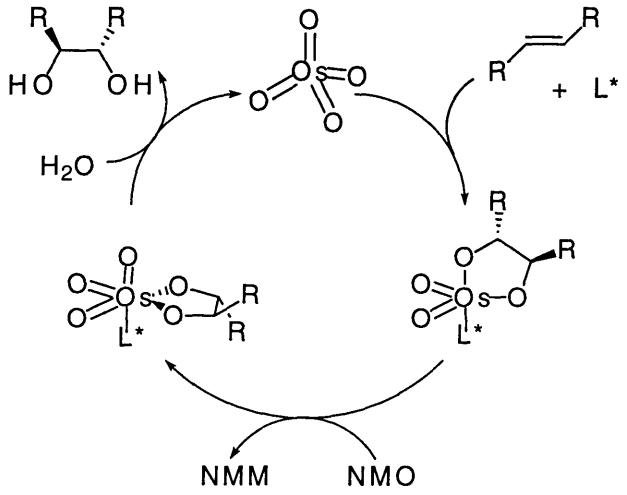
There are many important processes utilized extensively today industrially and in academic laboratories that were virtually ignored until a catalytic variant was developed. One example is the Wacker process, which today is used industrially to make roughly 4 million tons of aldehydes per year.[1] It has been known since the nineteenth century that aqueous palladium(II) chloride oxidizes ethylene to acetaldehyde stoichiometrically.[2] In the late 1950's it was found that the metal reagent could be recycled by reaction of the palladium(0) coproduct with copper(II) chloride to regenerate the active catalyst (Scheme 1).[3] The copper(II) is reduced to copper(I), which is air-sensitive and is oxidized back to copper(II) by reaction with oxygen. The resulting coupled reactions make the process inexpensive and useful both industrially and in academic laboratories for the synthesis of complex organic structures.[4]

Scheme 1



A second example of a reaction that has gained widespread use only after a catalytic variant was developed is the osmium-catalyzed asymmetric dihydroxylation of olefins. The cost and toxicity of osmium tetroxide prohibited the general use of the stoichiometric reaction[5] in organic synthesis until it was found that a catalytic amount of the metal can be used when *N*-methylmorpholine-*N*-oxide (NMO) is used as a cooxidant (Scheme 2).[6] Since then, this reaction has evolved into a very efficient and selective method that is used extensively in organic synthesis.[7]

Scheme 2

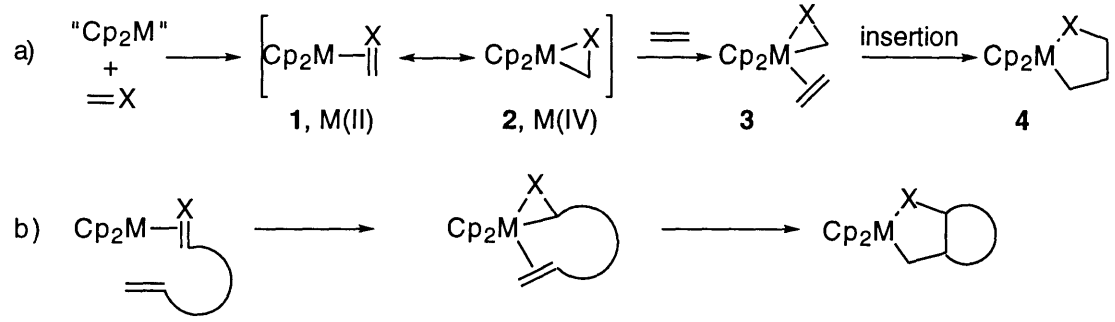


This thesis focuses both on the discovery of novel organometallic reactions that are of interest to organic chemists and on the development of catalytic variants with the goal of enabling their general use in the organic community. In particular, the research presented concentrates on the chemistry of early transition metal reductive cyclization.

The early transition metal-mediated reductive cyclization of unsaturated organic fragments encompasses a well documented class of reactions in which a metallacycle

containing a new carbon-carbon bond is formed.[8] The mechanism for group 4 mediated reductive cyclizations is shown in Scheme 3a. The active catalytic species is a metal complex in the +2 oxidation state which reacts with an unsaturated organic fragment to form a metal-olefin complex (for X = CH_2). Based on the Dewar-Chatt-Dunconson model, two resonance forms can be envisioned. In addition to a σ-bond of the π orbital of the olefin to the empty d orbital on the metal, there is also a π-backbonding interaction between a filled metal d orbital and the π* orbital on the olefin.[9] The two extreme resonance forms of the metal-olefin complex are the purely σ-complex **1** and a metallacyclopropane **2**. The chemistry of the metal-olefin complex (M = Ti, Zr, Hf) more strongly resembles that of **2**, which is in the +4 oxidation state. Metallacyclopropane **2** can then bind another unsaturated organic fragment to an open coordination site to form intermediate **3**. The second olefin can then undergo a 1,2-insertion into the metal-carbon bond to yield metallacycle **4**. In a variation of the above, if the two unsaturated organic fragments are tethered, then bicyclic metallacycles are formed (Scheme 3b).

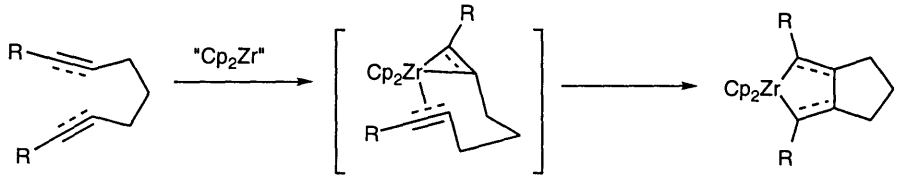
Scheme 3



Reductive cyclization is interesting from the point of view of the synthetic chemist because the metal mediates a reaction between two unactivated organic fragments. Thus, interesting net organic transformations that are difficult or impossible using traditional methods of organic synthesis are achieved. The stoichiometric intramolecular zirconocene-mediated reductive cyclizations of diynes,[10] dienes,[11] and enynes[12] were originally explored by Nugent and Negishi (Scheme 4). These

methodologies have been extended to other group 4 metals[13] and to the reductive cyclization of heteroatom-containing unsaturated fragments such as the intramolecular cyclizations of hydrazone/alkenes (or alkynes),[14] enones, and ynones.[15] These methods are powerful and several of the zirconocene-mediated methods have been used extensively in organic synthesis.[12] However, as discussed above, the development of catalytic versions of reductive cyclizations would be a significant improvement.

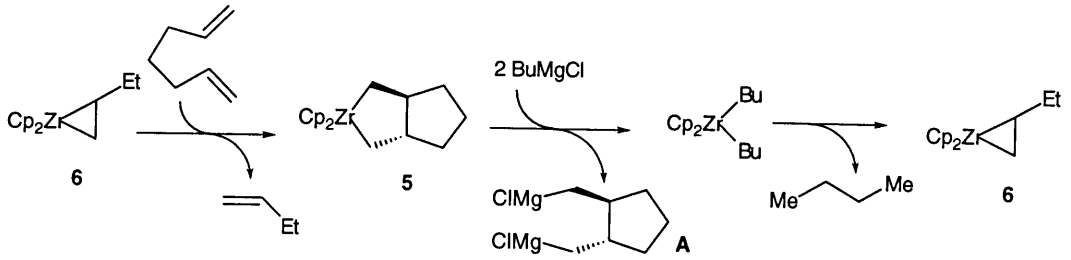
Scheme 4



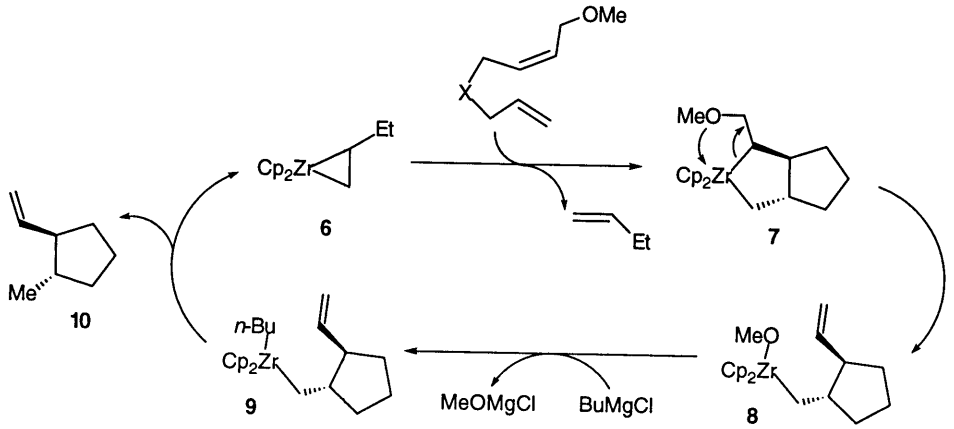
Several groups have developed catalytic methods for the reductive cyclization of dienes and enynes. The initial formation of the metallacyclic intermediates of these reactions parallels that seen in the stoichiometric procedures. In order to develop a viable catalytic reaction, a number of strategies have been employed to liberate the organic product and regenerate an active form of the catalyst. For the catalytic reductive cyclization of dienes, Waymouth employs *n*-butylmagnesium chloride to affect a transmetallation of the intermediate zirconacycle **5** to generate the di-Grignard species **A** and dibutylzirconocene, which eliminates butane to reform the zirconocene-butene adduct **6** (Scheme 5).[16] Mori uses a similar strategy for the catalytic formation of heterocycles from dienes.[17] In a related catalytic reductive cyclization of dienes which employs a Grignard to regenerate the catalyst, Waymouth has incorporated a suitably positioned ether moiety into the substrate so that the intermediate metallacycle **7** undergoes a β-alkoxide elimination to form zirconocene alkoxide **8** (Scheme 6).[18] This alkoxide reacts with a Grignard to form alkoxymagnesium chloride and the dialkyl-zirconocene intermediate **9**. The cyclopentane product **10** is formed

via a β-hydrogen abstraction process with concomitant regeneration of the zirconocene catalyst.

Scheme 5

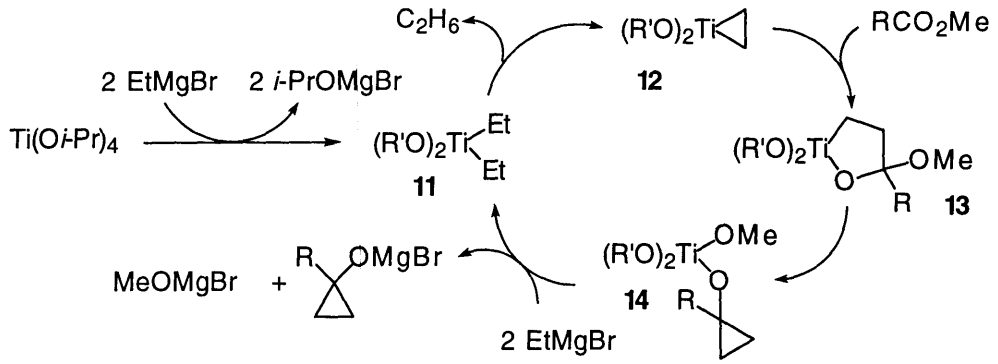


Scheme 6



Kulinkovich and coworkers have reported a related intermolecular reductive cyclization reaction utilizing a catalytic amount of $Ti(O\textit{i}Pr)_4$ and EtMgBr to convert esters to cyclopropanols (Scheme 7).[19] While this overall transformation is different than those discussed so far, the key reactions are similar to those employed in Waymouth's work. The proposed catalyticly active species is the diethyl-diisopropoxide titanium species **11**, which eliminates ethane to produce the titanacyclopropane **12**. Insertion of the carbonyl of the ester into the metallacycle produces the oxatitanacyclopentane **13**, which undergoes β-alkoxide elimination to form the coordinated cyclopentanol **14**. In a similar manner to the processes described so far, a Grignard reagent is used to convert this intermediate to the product and to regenerate the catalyst.

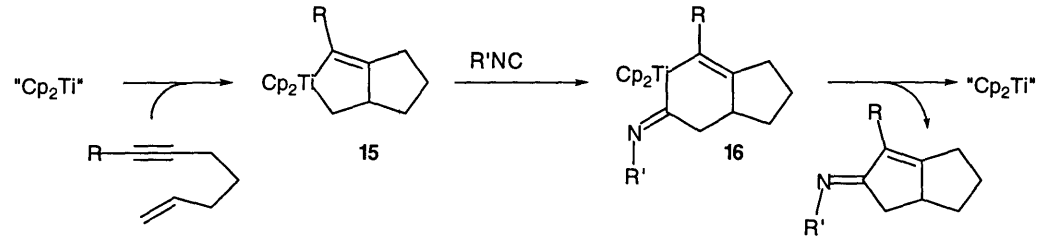
Scheme 7



In the Buchwald laboratory, a catalytic technique for the reductive cyclization of enynes to bicyclic cyclopentenones was developed which utilizes a different technique to liberate the organic product and regenerate the catalyst. Here, an isonitrile reacts with the intermediate metallacycle **15** to form titanacycle **16** (Scheme 8). Reductive elimination of the iminocyclopentene reforms the Ti(II) catalyst.[20]

In each of the cases discussed, the intermediate metallacycle generated from the reductive cyclization is converted into a reactive metal complex which either is or can be converted to the active form of the catalyst.

Scheme 8



The invention of novel metal-mediated organic transformations and their development into useful methodologies has been a major focus of the research in the Buchwald group. The overall goal of the research presented in this thesis has been the discovery of novel transition metal-mediated reductive cyclization reactions and the further elaboration of these reactions into viable and useful catalytic processes. Chapter 1 describes how the stoichiometric reductive cyclization of enones to bicyclic oxametallacycles reported by Whitby and coworkers was developed into a catalytic process to convert enones to cyclopentanols. The catalytic cycle was constructed by

combining Whitby's stoichiometric results with a σ-bond metathesis reaction discovered in the Buchwald laboratories. Chapter 2 describes a novel stoichiometric cyclocarbonylation of enones to γ-butyrolactones. This work was aimed at the formation of more functionalized and therefore potentially more useful products from reductive cyclization of enones. Finally, in Chapter 3, a catalytic version of the cyclocarbonylation reaction is presented.

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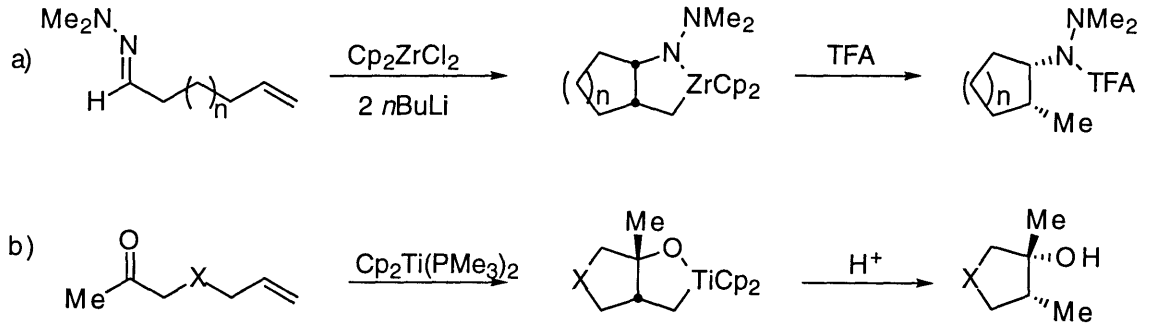
CHAPTER 1

THE DEVELOPMENT OF A METHOD FOR THE REDUCTIVE CYCLIZATION OF ENONES BY A TITANIUM CATALYST

Introduction

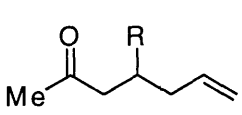
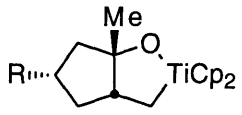
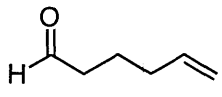
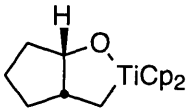
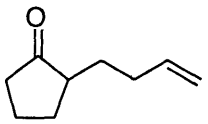
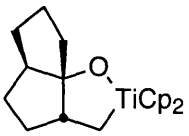
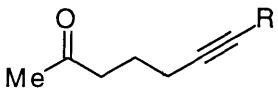
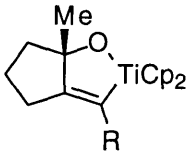
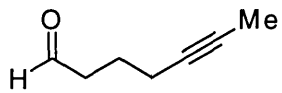
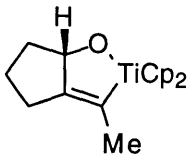
The intramolecular reductive coupling of diynes,[1] enynes,[2] and dienes[3] induced by low valent titanium and zirconium species has been known for some time. More recently, there have been reports of the stoichiometric reductive coupling of alkynes and alkenes with heteroatom-containing organic fragments using early transition metal complexes. Livinghouse has shown that hydrazones and alkenes or alkynes can be cyclized intramolecularly using a zirconocene reagent (Scheme 1a).[4] Whitby and Hewlett have demonstrated that a stoichiometric quantity of $Cp_2Ti(PMe_3)_2$ can be used to convert 1,6-enones to oxatitanabicyclopentanes in good yields (Scheme 1b). Hydrolysis of the resulting oxametallacycles results in the formation of cyclopentanols and the destruction of the titanocene reagent.[5] The results of Whitby's stoichiometric enone cyclization are shown in Table 1.

Scheme 1



We became interested in developing a catalytic variant of Whitby's enone cyclization reaction. Cleaving the exceptionally strong titanium-oxygen bond in these metallacycles in such a way as to lead to the regeneration of a catalytically active species posed a significant challenge. Titanium-oxygen bond energies are approximately 104 kcal/mol and are significantly stronger than the 50 to 70 kcal/mol strength of the titanium- and zirconium-carbon bonds which are broken in the early transition metal-catalyzed reductive cyclizations described in the introduction.[6]

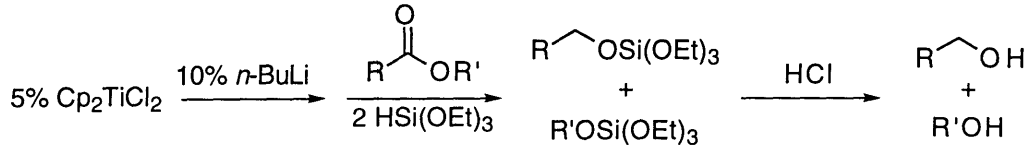
Table 1. Whitby's stoichiometric reductive cyclization of enones using $Cp_2Ti(PMe_3)_2$.[5]

entry	substrate	metallacycle	yield (%)
1		 R = H	76
2		R = Ph	83
3			76
4			53
5		 R = Me	60
6		R = H	35
7			79

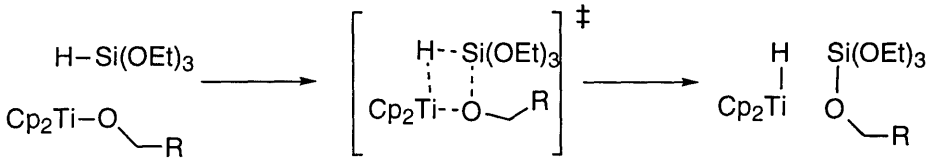
In order to break the Ti—O bond in a controlled and reductive manner, we turned to a proposed key step in a methodology previously developed in the Buchwald laboratories by Dr. Kristina Kreutzer and Dr. Scott Berk (Scheme 2).[7] In the titanocene-catalyzed conversion of esters to alcohols, a silane is utilized as the stoichiometric reductant. It is proposed that the Ti—O bond is cleaved by the Si—H bond of the silane via a 4-centered σ-bond metathesis process, with concommitant formation of Ti—H and Si—O bonds (Scheme 3). The reaction is driven by the strength of the Si—O bond (approx. 110 kcal/mol),[8] which is slightly stronger than the Ti—O bond. This reaction is extremely facile, occuring at or below room temperature. We envisioned using a silane to cleave the Ti—O bond of the oxatitanacycle **1** in a σ-bond metathesis process (Scheme 4). The resulting titanocene-alkyl-hydride **2** should

undergo facile reductive elimination to form the silylated cyclopentanol and to regenerate the catalyst.

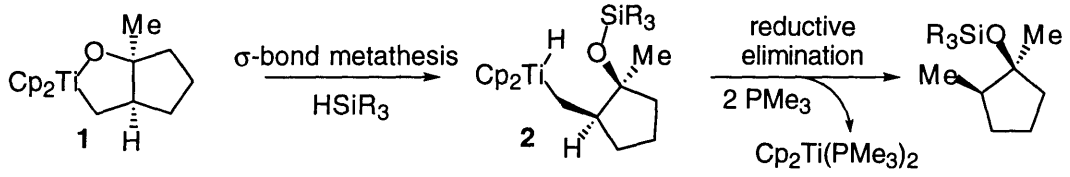
Scheme 2



Scheme 3



Scheme 4



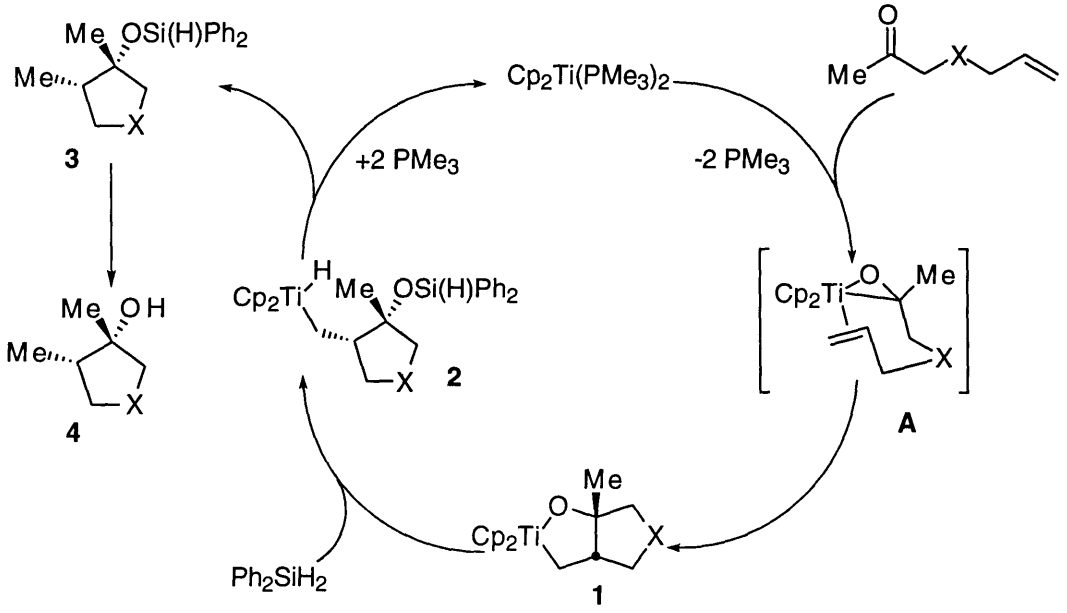
By using this σ-bond metathesis reaction, we have been able to develop a method for the conversion of enones to cyclopentanols using a catalytic amount of a titanocene complex. This chapter will describe the mechanism of this process and the subsequent optimization of the reaction conditions. The diastereoselectivities of the reaction of a number of substrate classes will be discussed as well as the scope and limitations of the method.

Results and Discussion

Using this key reactions discussed above, we propose the catalytic process for the conversion of enones to cyclopentanols shown in Scheme 5. Formation of titanacycle **1** proceeds by insertion of the coordinated olefin into the Ti-C bond of the nascent titanocene-ketone complex **A**. The silane then cleaves the Ti-O bond to form the titanocene alkyl hydride **2**, which undergoes ligand induced reductive elimination[9] to afford the silyl-protected cyclopentanol **3**, while regenerating the catalyst.

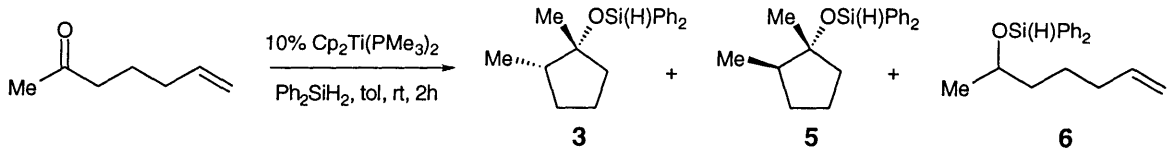
Hydrolysis of the silyl ether produces the cyclopentanol, **4**. We note that Crowe and Rachita independently developed a similar protocol based on the same key reactions.[10]

Scheme 5



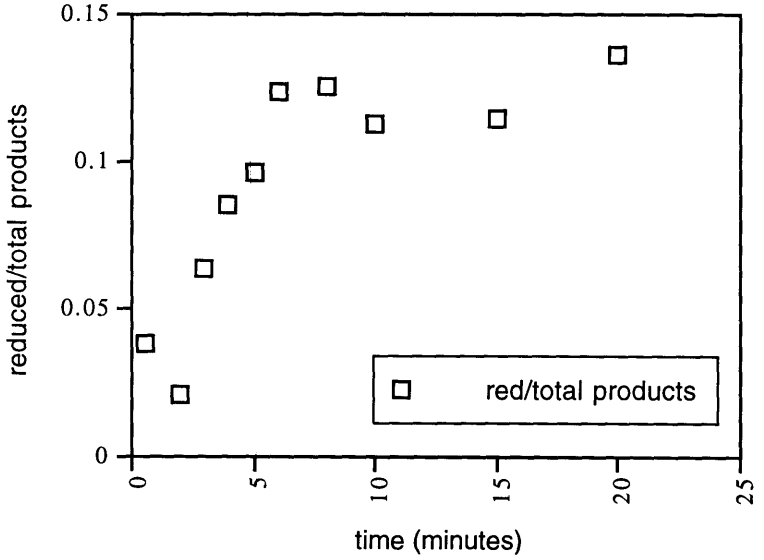
In initial experiments, the substrate, diphenylsilane, and 10 mol % $Cp_2Ti(PMe_3)_2$ were combined in toluene under anhydrous conditions. While this protocol was found to work extremely well for aldehyde-containing substrates (Table 2, entry 4), the cyclization of ketone-containing substrates under these conditions resulted in the formation of a mixture of products (Scheme 6). In addition to the desired silylated *cis*-cyclopentanol **3**, a small quantity of the *trans*-isomer **5** and a large amount of acyclic silyl ether **6**, resulting from the simple reduction of the carbonyl, were also produced. We first set out to determine the cause of the carbonyl reduction in an attempt to eliminate side product **6**.

Scheme 6

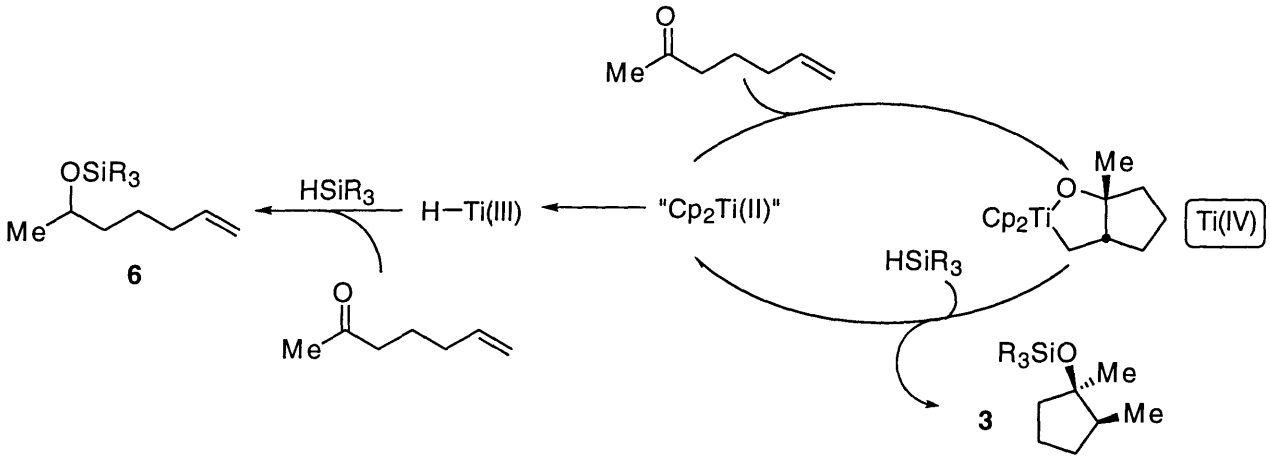


When the reaction is monitored by gas chromatography, initially only cyclized isomers **3** and **5** are observed. As the reaction progresses, the relative amount of **6** is initially observed to increase rapidly (see Figure 1). This suggests that the species responsible for the carbonyl reduction is different than the catalyst for the reductive cyclization; presumably, this species is generated by decomposition of the cyclization catalyst. We surmise that over the course of the reaction, some of the Ti(II) complex which acts as the cyclization catalyst is diverted from the catalytic cycle and converted to a Ti(III) hydride, which merely reduces the carbonyl (Scheme 7).[11] Harrod has shown that under similar conditions, diphenylsilane reacts with dimethyl titanocene to produce dimeric titanium(III) complexes, some of which are illustrated in Scheme 8.[11] Harrod showed that these complexes are active for the reduction and hydrosilation of olefins. We have found experimentally that the addition of excess trimethylphosphine to the reaction mixture reduces the amount of **6** produced, possibly by stabilizing the Ti(II) complex and preventing the decomposition to a Ti(III) hydride complex.

Figure 1: The relative amount of reduced product to total product.



Scheme 7



Scheme 8

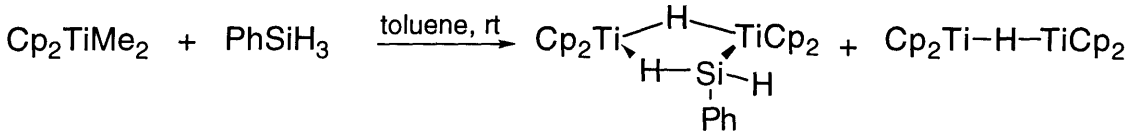


Table 2. Results of the catalytic reductive cyclization of enones.

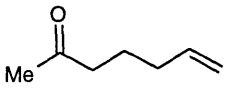
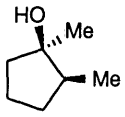
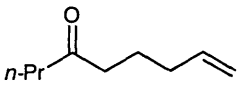
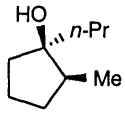
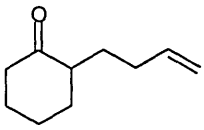
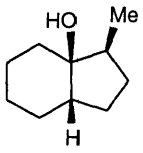
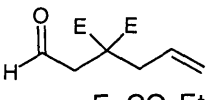
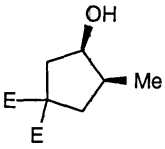
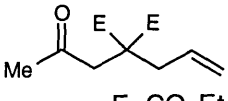
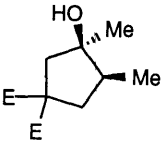
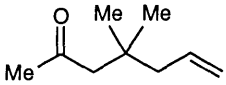
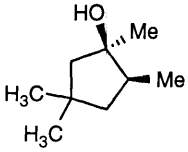
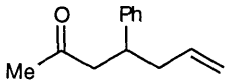
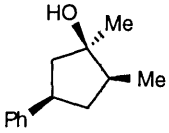
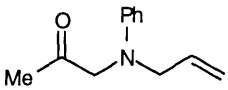
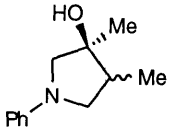
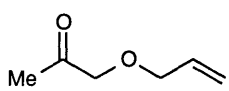
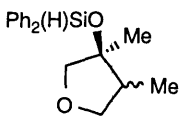
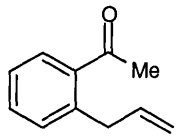
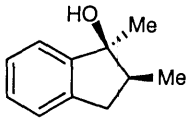
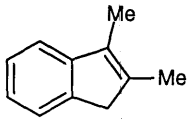
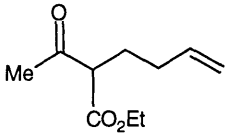
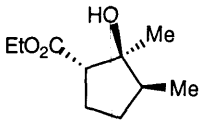
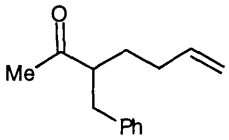
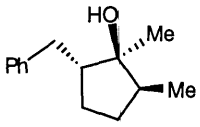
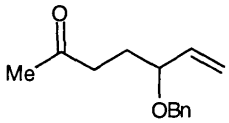
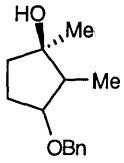
Entry	Enone	Product[a]	Workup[b]	Temp(°C)	Cyc./Red. (3+5):6[c]	*cis/trans* 3:5[c]	Yield (%)[d]
1			A	-20	17:1	43:1	64
2			A	-20	23:1	22:1	64
3[e]			A	-20	6:1	70:1	72[f]
4[g]			B	21	99:1	99:1	65
5			B	-20	99:1	10:1	68
6			A	-20	16:1	13:1	56
7			A	-20	99:1	2.5:1[k]	63[h]
8			A	-20	99:1	1:1	75[i]
9			C	-20	80:1	3:2	72[j]

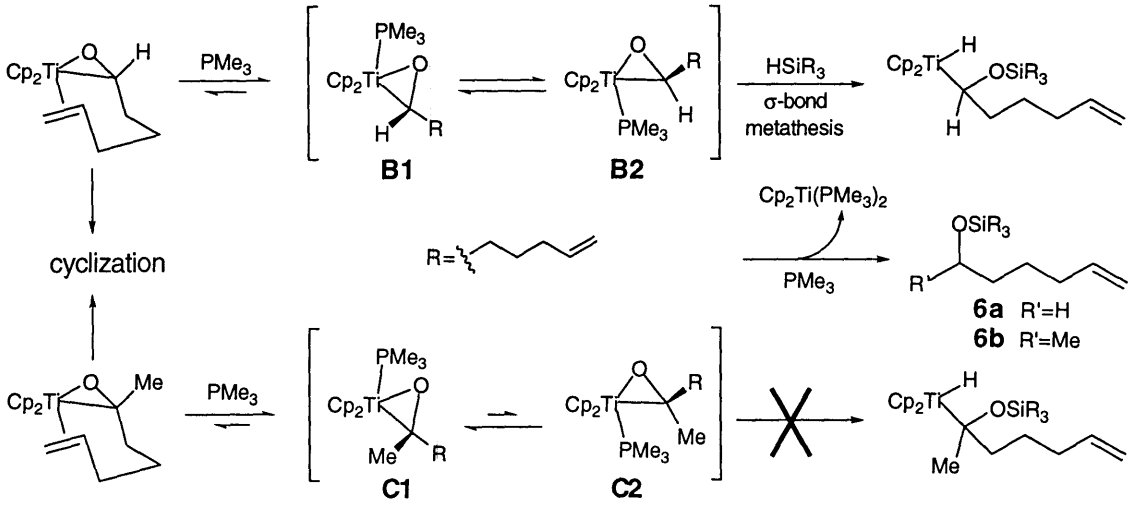
Table 2. Continued

Entry	Enone	Product[a]	Workup[b]	Temp(°C)	Cyc./Red. (3+5):6[c]	*cis/trans* 3:5[c]	Yield (%)[d]
10			D	-20	99:1	99:1	86
			A	-20	n. a.	99:1	71
11			B	21	99:1	90:1[k]	78
12			A	21	99:1	20:1[k]	71
13			B	21	3:1	3:2[k]	50[l]
				-20	8.5:1	4:1.6:1[k]	45[m]

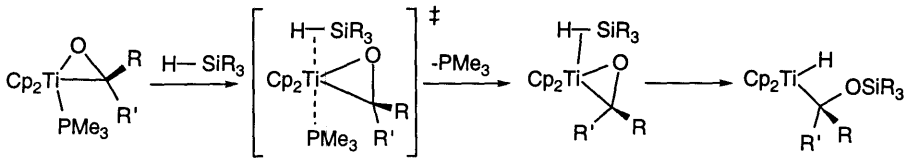
[a]Major isomer; [b]Workup A: HCl/ acetone, 3h; B: TFA/ H_2O/ THF/ CH_2Cl_2 0°C, 12h; C: silyl ether purified by distillation; D: TBAF/ THF, 15min . [c]As determined by GC. [d]Isolated yield of major isomer analytically pure except for entries 1, 2, and 6 which are of >95% purity as judged by GC and ^1H NMR analyses. The reported yields are an average of two or more runs. [e]$PhMeSiH_2$ was used instead of Ph_2SiH_2. [f]Isolated as a 9/1 mixture of **4** and **6** (see text). [g]No excess PMe_3 used with this substrate. [h]Yield of single isomer. [i]Total yield is 75%, but isomers were separated chromatographically in 37% and 38% yields. [j]Isolated as mixture of **4** and **5** (see text). [k]Ratio refers to the two (or three) major isomers observed (see text). The major isomer is shown. [l]Total yield is 50%, but isomers were separated chromatagraphically in 30% and 20% yields. [m]Total yield of the major two of the three isomers detected, which were also separated chromatographically in 32% and 13% yields. The third isomer co-elutes with the reduced products and was not isolated.

Experimentally we found that we can virtually eliminate the formation of the acyclic product **6** by modifying the reaction conditions by (a) adding excess trimethylphosphine to stabilize the Ti(II) catalyst, as described above, and (b) by running the reaction at a lower temperature (see Table 3). The optimal conditions that we have developed are 10 mol % $Cp_2Ti(PMe_3)_2$, 60 mol % trimethylphosphine, and 1.0 equivalent diphenylsilane at -20 °C. The results of the reaction under these conditions are shown in Table 2. It should be noted that under conditions employing excess PMe_3, reduction is the main pathway for aldehyde substrates. This contrasting behavior can be explained if the reduction can also occur through a second pathway as shown in Scheme 9. Here, the silane cleaves the titanium-oxygen bond in titanocene-ketone/aldehyde complexes **B** or **C**, followed by reductive elimination of the acyclic reduced product. We believe that this second pathway only occurs through the intermediates **B** and **C**, since presumably cyclization occurs preferentially as soon as the olefin coordinates to the titanocene-ketone/aldehyde complex. The addition of excess trimethylphosphine will favor the formation of the PMe_3 adducts of **B** and **C**. In both instances, as is shown in Scheme 9a, two geometric isomers of the adducts are possible. We speculate that only the isomer with the PMe_3 group coordinated *anti* to the oxygen can undergo the σ-bond metathesis reaction. A possible explanation is that the silane precoordinates to the complex *syn* to the oxygen before σ-bond metathesis occurs (see Scheme 9b).[12] For enal complexes, both **B1** and **B2** are viable, and the reaction may proceed via a σ-bond metathesis process through **B2**, leading to side product **6a**. For enones, **C2** is destabilized for steric reasons (see Scheme 9c), and the quantity of **6b** produced is minimal.

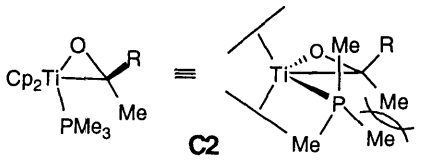
Scheme 9a



Scheme 9b



Scheme 9c



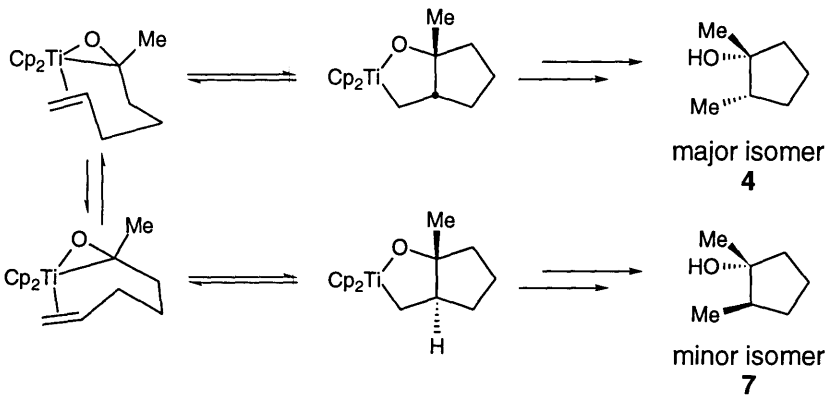
Diastereoselectivity of Cyclization -- Effect of Substituents

In addition to exploring the mechanism of this cyclization reaction, we have also investigated the cyclization of a range of substrates in order to study the diastereoselectivity of the transformation. Two aspects of the diastereoselectivity will be discussed: the formation of new chiral centers at the ring junction of the intermediate metallacycles and the effect of preexisting chiral centers on the diastereoselectivity of the cyclization.

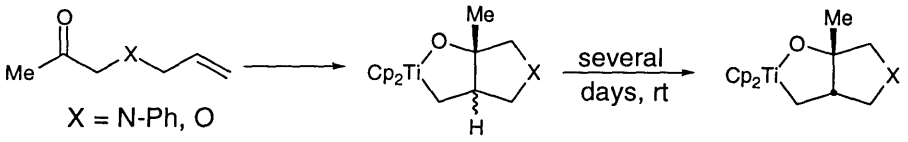
Whitby et al. found that the stoichiometric reaction of achiral substrates is completely diastereoselective; only the thermodynamically favored *cis*-fused

metallacycle is formed.[5] The diastereoselectivity of the catalytic reaction for achiral substrates, while not complete, is generally very good (Table 2, entries 1-4 and 10). Though *cis*-cyclopentanol **4**, which is formed via a *cis*-fused metallacycle, is the major product formed in the catalytic reaction, small amounts of isomer **7**, formed via a *trans*-fused metallacycle, are also detected in most cases (Scheme 10). In the stoichiometric reaction, the steps leading to metallacycle formation are reversible, so only the thermodynamically favored product is formed. During the catalytic process, the organic fragment can be cleaved from the intermediate titanium complex by the silane before complete equilibration to the thermodynamic product can occur, and a mixture of isomers is produced.[13] For substrates containing a heteroatom in the backbone (Table 2, entries 8 and 9), little or no diastereoselectivity is observed. The stoiciometric reactions of these substrates show no kinetic selectivity, but the resulting metallacycles equilibrate to the more stable *cis*-isomer over several days (Scheme 11).[14,15] Hence, the nonselective results of the catalytic reactions employing these substrates are not surprising.

Scheme 10



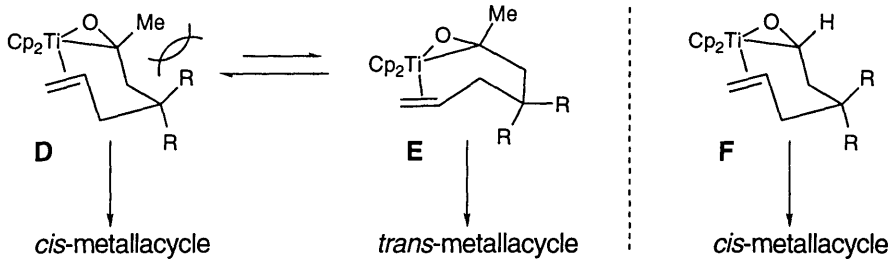
Scheme 11



The interplay of kinetic and thermodynamic factors also contributes to the slight decrease in diastereoselectivity for the cyclization of enones that are disubstituted in

the β-position (Table 2, entries 5 and 6). Scheme 12 shows that the "chair-like" intermediate **D** which leads to the *cis*-fused metallacycle contains a destabilizing pseudo-1,3-diaxial interaction between the substituent on the β-position and the methyl group. This decreases the energy difference between **D** and the "boat-like" intermediate **E**, leading to increased formation of the *trans*-product. For an aldehyde that is disubstituted in the β-position (Table 2, entry 4), there is a significantly less severe pseudo-1,3-diaxial interaction in intermediate **F**, and excellent selectivity is observed.

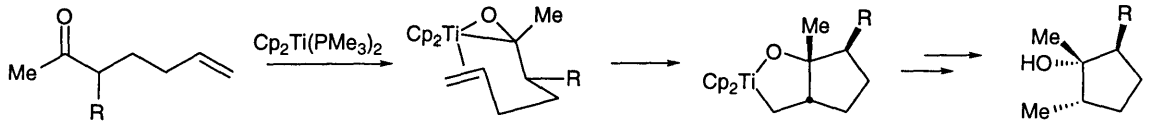
Scheme 12



The acetophenone derivative (Table 2, entry 10) is interesting in that it is cyclized by this protocol in high yield and with excellent selectively to give only one observable silyl ether product. We believe that the cyclization is enhanced by the phenyl ring in the backbone of the substrate which holds the two reactive unsaturated organic fragments in close proximity, thus increasing the effective molarity of the reactants.[16] Note that depending on the method of workup employed, either the bicyclic cyclopentanol or the dimethyl indene can be produced in good yield.

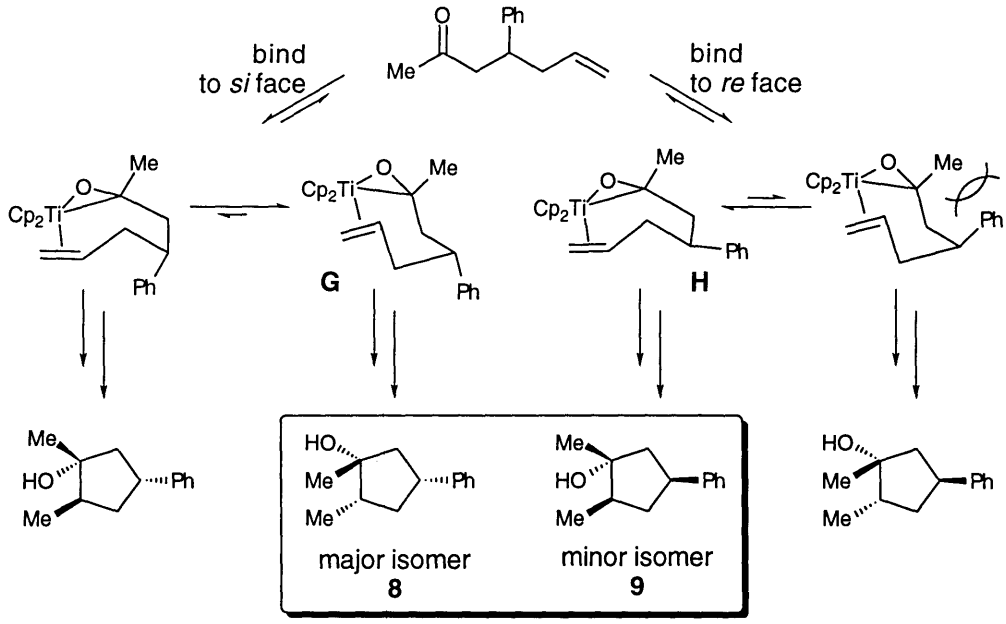
Chiral substrates with single substituents on the backbone (Table 2, entries 7, 11, 12, and 13) can form four isomers. Substrates with substituents α, β, and γ to the carbonyl were studied. In these cases, modest to excellent diastereoselectivity is observed.

Scheme 13



Substrates with a single substituent in the position α to the carbonyl (Table 2, entries 11 and 12) proceed with good to excellent diasteroselectivity, and one isomeric product is primarily observed. As shown in Scheme 13, the substituent is placed preferentially in the equatorial position of the chair-like intermediate. Cleavage of the organic fragment from the resulting metallacycle followed by hydrodesilylation provides the observed cyclopentanol. If the α substituent is an ethyl ester (Table 2, entry 11), cyclization occurs with a 90:1 diastereoselectiviy; if it is a benzyl group (Table 2, entry 12), the diastereoselectivity is 20:1. In addition, Crowe and Rachita report that the cyclization of an aldehyde with a methyl group α to the carbonyl proceeds with the formation of two diastereomers with a 4:1 selectivity.[10]

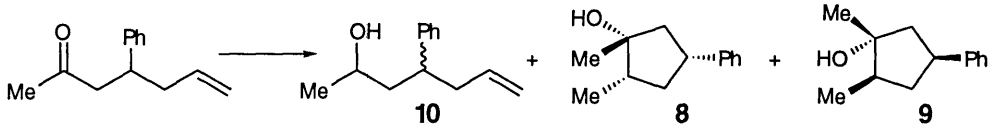
Scheme 14



Scheme 14 shows that in the reaction of 4-phenyl-6-heptene-2-one (Table 2, entry 7), which has a phenyl group in the β-position, two of the four possible isomers

are formed (assignment by nOe analysis). Additionally, as shown in Table 3, the ratio of the isomers which are observed is temperature dependent. A possible explanation for these findings is that the titanocene moiety can initially bind to either of the two diastereotopic faces of the carbonyl. If the titanium binds to the *si* face, reaction via the chair-like intermediate **G** is favored, and the major isomer **8** is formed. If the titanium binds to the *re* face, reaction *via* the boat-like intermediate **H** is favored due to the severe pseudo 1,3-diaxial interaction in the chair-like intermediate, and the minor isomer **9** is formed. The temperature dependence of the isomeric ratio may result from the sensitivity of the rate of the equilibration between the *re* and *si* faces on temperature. At high temperatures, the equilibration between the diastereomeric complexes is fast, so that the proportion of the isomer formed *via* the thermodynamically favored intermediate increases.[17] At low temperatures, the organic fragment is cleaved from the metal before equilibration is complete, so that a mixture of isomers is produced.

Table 3. The effect of temperature on product distribution.

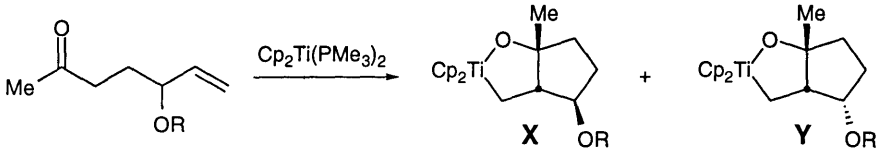


temperature °C	cis / trans [8:9]	cyclized / reduced [(8+9):10]	isolated yield of 8 (%)
-20	2.2:1	99:1	63
-5	3:1	65:1	59
0	3.5:1	46:1	50
21	5:1	10:1	63
50	6:1	10:1	55

Cyclizations of substrates which have γ substituents proceed with very low levels of diastereoselectivity. Several substrates have been cyclized using a stiochiometric quantity of $Cp_2Ti(PMe_3)_2$; in each case an *ca.* 1:1 mixture of *cis*-metallacycles is observed. For substrates with smaller γ substituents, such as OAc

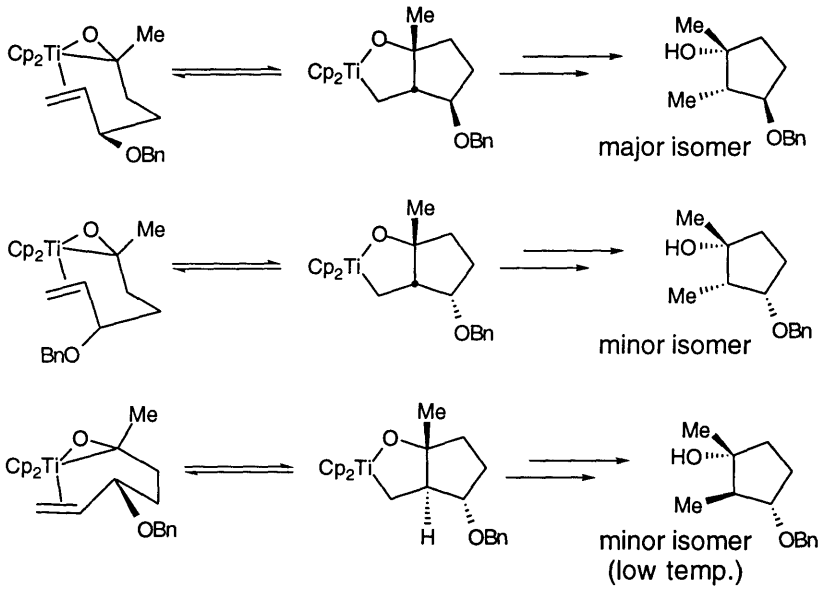
and OBn, the product with the substituent on the *exo*-face is slightly favored. When the substituent is the larger triisopropylsilyl group, the metallacycle with the *endo* substituent is slightly favored (Scheme 15). The benzyl substituted substrate (Table 2, entry 13) has been cyclized under catalytic conditions, and at room temperature two products are produced which corresponded to the intermediate *cis*-metallacycles (Scheme 16). When the reaction is run at -20°C, a third isomer can be identified.

Scheme 15



R =	Ac	**X** / **Y**= 1.4:1
	Bn	1.3:1
	TIPS	1:1.4

Scheme 16

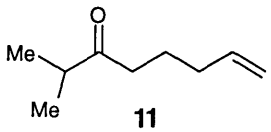


Scope and Limitations

We have explored the scope of this cyclization methodology, and we found that these reactions are in general very sensitive to the steric bulk of the substrates. While

methyl and *n*-propyl ketones (Table I, entries 1 and 2) cyclize smoothly under the conditions outlined above, more sterically congested ketones, such as entry 3, require a smaller silane for catalysis. However, we observe that small silanes, such as methylphenylsilane, increase the amount of acyclic reduction products formed. Enones with *iso*-propyl and phenyl substituents on the ketone (**11** and **12**, Scheme 17) form metallacycles stoichiometrically, but the substituents are too bulky to allow facile σ-bond metathesis without significant carbonyl reduction under catalytic conditions. Both Whitby[5] and Crowe[10] have found that substrates that would give rise to cyclohexanols do not cyclize at all, even stoichiometrically; we found that 7-hexen-2-one, **13**, fails to cyclize. We have attempted to favor ring closure by incorporating substituents on the backbone; however, compounds **14**, **15** and **16** also fail to form metallacycles when treated with a stoichiometric amount of $Cp_2Ti(PMe_3)_2$. Furthermore, substitution on the alkene is not tolerated by this protocol; enones **17**, **18**, and **19** do not form metallacycles when treated with a stoichiometric quantity of $Cp_2Ti(PMe_3)_2$.

Scheme 17



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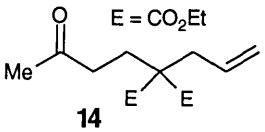
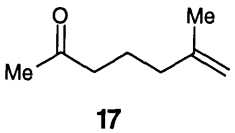
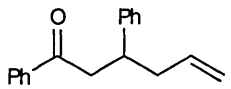


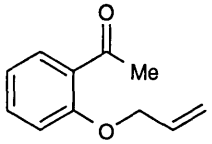
14



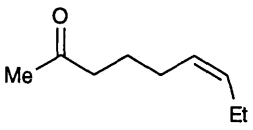
17



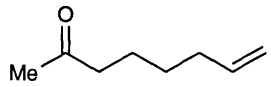
12



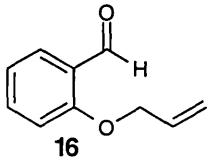
15



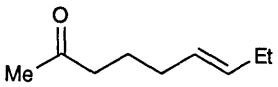
18



13



16



19

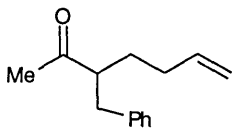
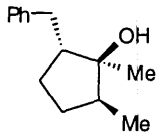
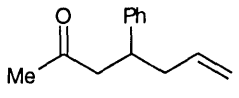
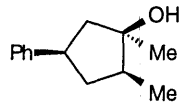
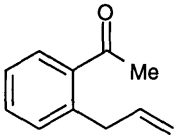
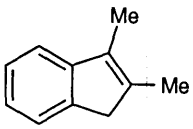
The moderate degree of functional group tolerance of this methodology should be noted. Often early transition metal catalysts are incompatible with polar functional groups; however, in the transformation reported here, enones containing esters and

allyl ethers are tolerated (Table 2, Entries 4, 5, and 9). Additionally, the cyclization of the β-keto ester (Table 2, Entry 11) shows that the acidic proton is not detrimental to cyclization.

In Situ Generation of the Catalyst

A limitation to the use of this methodology is that the catalyst, $Cp_2Ti(PMe_3)_2$, is a pyrophoric, air- and moisture-sensitive complex that must be stored and handled in a glove box under argon. In order to make this methodology more practical, a protocol for the *in situ* generation of the catalyst utilizing the inexpensive, air- and moisture-stable Cp_2TiCl_2 was developed. Whitby originally synthesized the oxatitanacycles from $Cp_2Ti(PMe_3)_2$ formed *in situ* from Cp_2TiCl_2 and PMe_3.[5] We found that a variation of this method, which is experimentally less complicated, forms a viable catalyst that is active at 15 mol %.[18] Treating finely ground Cp_2TiCl_2 with *n*-BuLi and excess PMe_3 in toluene produced $Cp_2Ti(PMe_3)_2$, which was then cannula filtered into a separate vessel containing 7.5 equivalents of the enone. This solution was then cooled to the desired temperature and the silane was added. Because the formation of $Cp_2Ti(PMe_3)_2$ is not quantitative (upon filtration, some titanium residue is left behind), a slightly higher catalyst loading is necessary. Without the filtration step, products resulting from carbonyl reduction are observed. Attempts to form the oxametallacycles directly from Cp_2TiCl_2 and *n*-BuLi were unsuccessful. Table 4 compares the results obtained using the two methods for catalyst generation with several substrates.

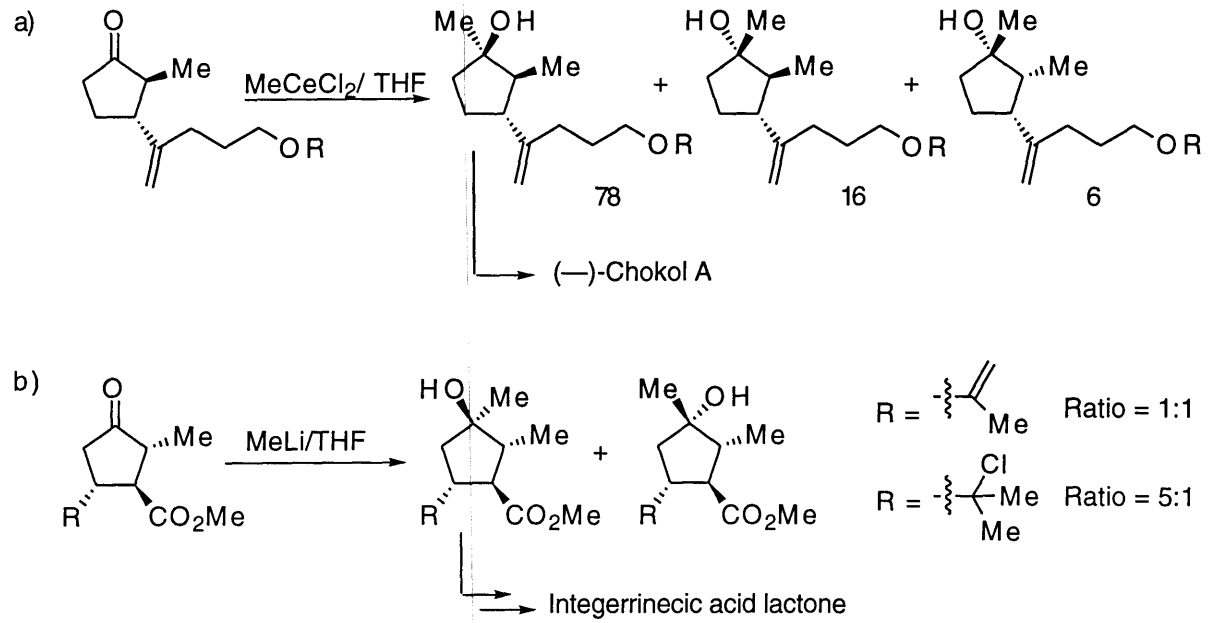
Table 4. Results of the reductive cyclizations with *in situ* generation of the catalyst.

enone	isolated product	*cis/trans* (see Table I)	yield (%) using *in situ* method	yield using $Cp_2Ti(PMe_3)_2$
		17:1	74	75
		2.5:1	60	63
		99:1 for silyl ether intermediate	72	71

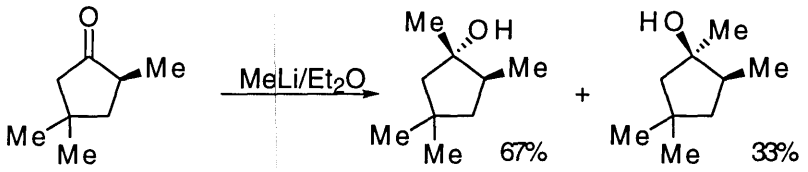
Comparison to Other Cyclopentanol Syntheses

The more conventional entry into the cyclopentanols of the type synthesized using this methodology is by the reaction of the corresponding cyclopentanone with an organolithium, organomagnesium, or organocerium reagent. Two recent examples that demonstrate the use of this route to cyclopentanols in the total syntheses of (—)-Chokol A[19] and (+)-integerrinecic acid lactone[20] are shown in Scheme 18 (a and b respectively). While this is a powerful method, these examples show that complete diastereoselectivity is not always achieved; Scheme 18b also demonstrates that the diastereoselctivities are very sensitive to the substituents on the cyclopentanone. Rei has conducted detailed studies on the reactivity of a number of substituted cyclopentanols with MeLi and found that even in simple cases that only moderate diastereoselectivities are achieved (Scheme 19).[21]

Scheme 18

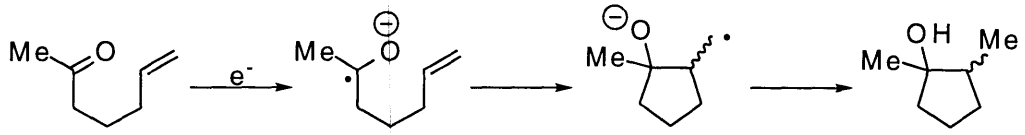


Scheme 19



A great deal of effort has been devoted to the development of a different strategy for the construction of substituted cyclopentanols utilizing a methodology similar to the titanocene catalyzed-reductive cyclization that we have described. This method employs a reductive cyclization of enones *via* an anion radical cyclization (Scheme 20). This transformation has been carried out by electroreductive,[22-25] photoreductive,[26,27] and chemoreductive[28-30] methods.

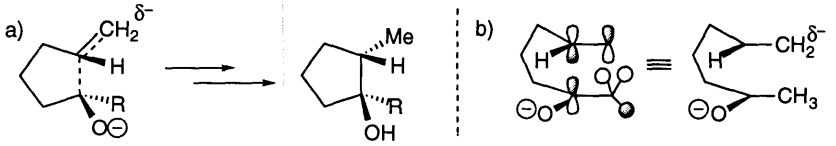
Scheme 20



Stereocontrol in most radical anion cyclization methods is excellent, but in contrast to our titanocene catalyzed reductive cyclization methodology, the *trans*-2-

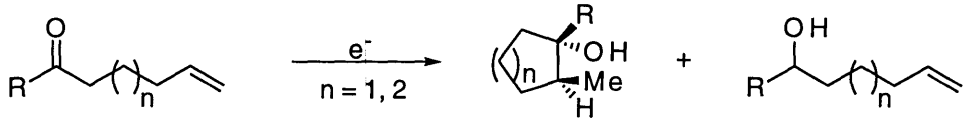
methyl cyclopentanols are the major products. Two reasons for the observed selectivity have been suggested. A repulsive electrostatic interaction between the oxygen and the methylene group in the transition state has been implicated, since both groups carry a negative charge (Scheme 21a).[22,31,32] A second explanation, which was originally proposed for neutral radical cyclizations but has been applied to radical anion cyclizations, suggests that there is a favorable secondary orbital interaction between the developing radical center and the alkyl group on the ketone (Scheme 21b).[32-34] Since radical anion cyclizations are more diastereoselective than their neutral counterparts, it is probable that both of these factors contribute to the high levels of diastereoselectivity in the anion cases.[29,32]

Scheme 21



While the stereochemistry of the cyclopentanols resulting from radical cyclizations differ from that obtained from our titanocene catalyzed cyclization, both systems suffer to some extent from reduction of the carbonyl to form the acyclic alcohol (Scheme 22).[22] However, an advantage of radical cyclizations is that in contrast to the titanocene-catalyzed enone cyclizations, cyclohexanols can also be generated,[22,29] although in these cases reduction of the carbonyl is more of a problem.

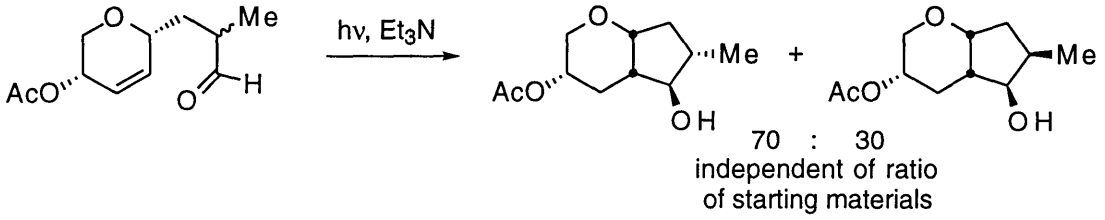
Scheme 22



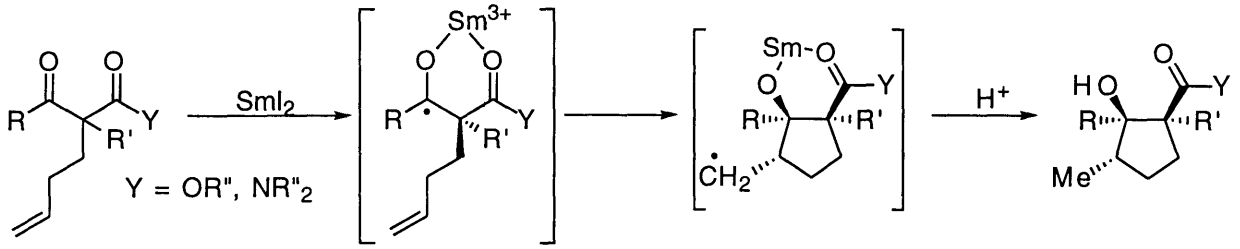
Another difference between these two enone cyclization methologies is the control of remote stereocenters. In most cases the stereochemistry around the newly formed carbon-carbon bond is good to excellent in both the titanocene-catalyzed reductive cyclization and the radical cyclizations; however, the control of remote

centers in the radical cyclizations is low compared to that of our titanocene-catalyzed reaction (*vide supra*). For example, Cossy has observed moderate diastereoselectivity for the photoinduced radical cyclization of carbohydrate-based systems as shown in Scheme 23.[26] In contrast, the diastereocontrol of centers α-to the carbonyl in our titanocene catalyzed cyclization is excellent. Molander and coworkers have overcome the low diastereoselectivities by using chelation control in samarium(II)-mediated cyclizations to direct the stereochemistry of the substituent α to the carbonyl (Scheme 24).[28]

Scheme 23

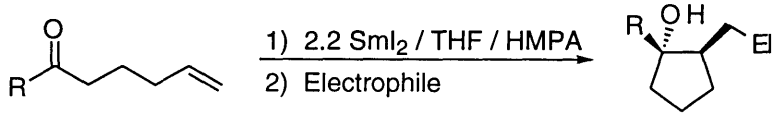


Scheme 24



A major drawback to the titanocene-catalyzed cyclization described in this chapter is the inablilty to produce more highly functionalized products. In radical induced cyclizations it is possible to trap the methylene radical to add functionality to the methyl group generated from the olefin. For example, Molander has found that the methylene radical produced in the samarium(II)-mediated radical cyclizations of enones can be trapped by a number of electrophiles (Scheme 25).[29]

Scheme 25



Finally, it is instructive to compare our work to the method for the titanocene catalyzed reductive cyclization reaction independently developed by Crowe and coworkers.[10] Crowe's protocol uses twice the quantity of catalyst (20 mol %) and works well for aldehyde-containing substrates. Their use of triethoxysilane, which is a fairly hazardous compound,[35] lends itself to ease in isolation of the products, since the resulting silyl ethers are stable to silica gel chromatography. Diphenylsilyl ethers produced by our method are not stable to silica gel and must be hydrodesilylated before analytically pure products can be isolated. Our protocol is preferred for the cyclization of ketone containing substrates, since excessive carbonyl reduction is avoided.

The titanocene-catalyzed cycloreduction of enones is a complementary method to those that exist for the construction of cyclopentanols. The intermediacy of the metallacycle, however, provides some advantages over the radical anion cyclizations. As previously described, the intermediate metallacycle enforces the stereochemistry at remote centers. The metallacyclic intermediate also gives our methodolgy a handle for potential improvements. The titanium-carbon bond in the intermediate metallacycle is the key to further functionalization of the product; this will be described in Chapter 2. Finally, the use of titanocene catalysts allows for the possibility of replacing the cyclopentadienyl ligands with chiral ligands to generate an enantioselective process (see Chapter 3).

Experimental Prodedures

General Considerations. All manipulations involving air-sensitive materials were conducted in a Vacuum Atmospheres glovebox under an atmosphere of argon or using standard Schlenk techniques under argon. THF was distilled under argon from sodium/benzophenone before use. Toluene was distilled under argon from molten sodium, and CH_2Cl_2 was distilled under nitrogen from CaH_2. Bis(trimethylphosphine)titanocene, $Cp_2Ti(PMe_3)_2$ was prepared from titanocene dichloride (obtained from Boulder Scientific, Boulder, CO) by the procedure of Binger et al.,[36] and was stored in a glovebox under argon. The enone ethyl-6-hepten-2-one -3-carboxylate (table I, entry 11)[37] was prepared from ethyl acetoacetate and 4-bromobutene (NaOEt, HOEt, reflux), and the enones 6-hepten-2-one,[38] 8-nonen-4-one,[39] and 2-homoallylcyclohexanone[38] (table I, entries 1,2, and 3) were prepared using the same procedure with the appropriate ethyl acetate followed by decarboxylation. Enones 4,4-dimethyl-6-hepten-2-one and 4-phenyl-6-hepten-2-one (table I, entries 6 and 7) were prepared from the allylation of the appropriate α,β-unsaturated ketone with allyltrimethylsilane and $TiCl_4$.[40] Enone diethyl-5-hexen-1-al-3,3-dicarboxylate (table I, entry 4) was prepared by the procedure of Bernard et al.[41] Allyl acetonyl ether (table I, entry 9) was prepared according to the procedure of Kachinsky and Salomon[42] (NaH, allyl alcohol and propylene oxide, followed by PCC oxidation). *Ortho*-allylacetophenone (table I, entry 10) was prepared by a Stille coupling of allyltributyltin and *o*-bromoacetophenone.[43] Synthesis of previously unreported enone substrates are described below. All other reagents were available from commercial sources and were used without further purification, unless otherwise noted.

Flash chromatography was performed on E. M. Science Kieselgel 60 (230-400 mesh). Yields, unless otherwise stated, refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^1H NMR analysis, and in the cases of unknown compounds, elemental analysis. Yields indicated in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly. All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopies. Previously unreported compounds were also characterized by elemental analysis (E & R Analytical Laboratory, Inc.). Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian XL-500, or a Varian Unity 300. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; qd, quartet of doublets; m, multiplet. All ^1H NMR spectra are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer. Gas chromatography (GC) analysis were performed on a Hewlett-Packard 5890 gas chromatograph with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase.

Preparation of Enone Starting Materials. Diethyl-6-hepten-2-one-4,4-dicarboxylate (Table 2, Entry 5): Using a modified Wacker oxidation,[44] palladium(II) chloride (1.1 g, 6 mmol), copper(I) chloride (2.97 g, 30 mmol), dimethylformamide (15 mL), and water (2.1 mL) were added to a flask and stirred under a balloon of oxygen for 2 h (until the solution turned green in color). Diethyl allylmalonate (6 mL, 30 mmol) was added and the solution was stirred for 18 h. Following the addition of H_2O (30 mL), the mixture was extracted with 3 x 30 mL Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, and the

solvent was removed *in vacuo*. Purification of the resulting yellow oil by flash chromatography (hexane: ethyl acetate = 4: 1) yielded 3.7 g (56% yield) of a clear oil. Of this, 2 g (9 mmol) were added to an oven-dried Schlenk flask containing a slurry of NaH (0.5 g, 14 mmol) and toluene (50 mL) and heated to 65°C for 0.5 h. The mixture was cooled to room temperature and allyl bromide (0.66 mL, 11 mmol) was added. The solution was stirred at 85 °C for 12 h. After cooling the solution to room temperature, *p*-toluene-sulfonic acid (0.6 g, 3 mmol) was added and the mixture was stirred for 10 min then filtered through celite. The solvent was removed *in vacuo* and purification by flash chromatography (hexane: ethyl acetate = 9:1) afforded 0.7 g (34% yield) of a colorless oil. ^{1}H NMR (300 MHz, C_6D_6): δ 5.71 (m, 1 H); 4.92 (m, 2 H); 3.99 (q, J = 7.2 Hz, 4 H); 3.05 (s, 2 H); 3.03 (d, J = 7.3 Hz, 2 H); 1.64 (s, 3 H); 0.94 (t, J = 7.2 Hz, 6 H). ^{13}C NMR (75 MHz, C_6D_6): δ 203.8, 170.2, 133.8, 118.9, 61.4, 55.5, 45.8, 38.1, 29.8, 14.0. IR (neat): 2892, 2938, 1732, 1640, 1466, 1407, 1366, 1287, 1200, 1095, 925. Anal. calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87. Found: C, 61.06; H, 8.13.

***N*-allyl-*N*-acetonyl aniline (Table 2, Entry 8)**: A modified version of Watanabe's procedure[45] was used. Under an argon atmosphere, *N*-allyl aniline (4,4 mL, 25 mmol), propargyl alcohol (1.5 mL, 25 mmol), cadmium acetate dihydrate (12 mg, 0.04 mmol) and zinc acetate dihydrate (12 mg, 0.05 mmol) were added to a Schlenk flask fitted with a reflux condenser and heated to 80°C for 3 d. The reaction products were first purified by vacuum distillation, then the fraction containing the title compound was further purified by flash chromatography (hexane: ethyl acetate = 9: 1), which afforded 0.95 g (20% yield) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (dd, J = 8.9 Hz, J = 7.3 Hz, 2 H); 6.73 (t, J = 7.3 Hz, 1 H); 6.58 (d, J = 8.9 Hz, 2 H); 5.85 (m, 1 H); 5.17 (m, 2 H); 3.99 (d, J = 4.2 Hz, 2 H); 3.98 (s 2 H); 2.15 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 148.0, 133.4, 129.2, 117.3, 116.7, 112.2, 60.7,

54.3, 26.9. IR (neat): 3040, 2917, 1726, 1675, 1599, 1506, 1383, 1354, 1233, 1165, 994, 692, 748. Anal. calcd for $C_{12}H_{15}NO$: C, 76.14; H, 7.99. Found: C, 76.32; H, 8.03.

3-Benzyl-6-hepten-2-one (Table 2, Entry 12): To a flame-dried Schlenk flask containing NaH (0.26g, 11 mmol) and THF (20 mL), *tert*-butyl 2-acetyl-5-hexenoate[46] (2.3g, 11 mmol) was added. The mixture was stirred at room temperature for 1 h, then benzyl bromide (1.3 mL, 11 mmol) was added and the flask was fitted with a reflux condenser and refluxed for 15 h. The mixture was cooled, quenched with H_2O (50 mL), and extracted with 3 x 30 mL ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and the 3 benzyl-3-(*tert*-butoxycarbonyl)-6-hepteneoate was purified by Kugelrohr distillation. A solution of *p*-toluene-sulfonic acid monohydrate (65 mg, 0.34 mmol) in toluene (30 mL) under argon in a 50 mL round-bottom flask equipped with a Dean-Stark trap and reflux condenser was heated at reflux for 1.5 h. The solution was cooled to room temperature and all of the 3 benzyl-3-(*tert*-butoxycarbonyl)-6-hepteneoate from the previous step was added. The mixture was heated at reflux for 5 h, then it was cooled to room temperature overnight. The solution was diluted with 30 mL diethyl ether, washed with 30 mL saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (hexane: ethyl acetate = 19: 1) to yield 1.1g (50% yield) of a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.2 (m, 5 H); 5.72 (m, 1 H); 4.99 (m, 2 H); 2.74 (m, 2 H); 2.69 (m, 1 H); 2.03 (m, 2 H); 1.98 (s, 3 H); 1.75 (m, 1 H); 1.51 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.2, 139.4, 137.8, 128.8, 128.5, 126.3, 115.3, 53.8, 38.0, 31.4, 30.5, 30.4. IR (neat): 3027, 2926, 1713, 1496, 1453, 1351, 1162, 914, 753, 700. Anal. calcd for $C_{14}H_{18}O$: C, 83.11; H, 8.97. Found: C, 83.35; H, 8.92.

5-Benzyloxy-6-hepten-2-one (Table 2, Entry 13). 1,6-Heptadien-3-ol was prepared by a method adapted from that of Ireland[47] by the addition of vinylmagnesium bromide to the crude aldehyde product generated by the Swern oxidation of 4-penten-1-ol. The 1,6-heptadien-3-ol (1.6 g, 14 mmol) was added to a flame-dried Schlenk flask under argon containing a slurry of NaH (0.5 g, 20 mmol) and THF (20 mL) and fitted with a reflux condenser. The mixture was heated to reflux for 20 min, benzyl bromide (1.62 mL, 14 mmol) was added, and the solution was heated at reflux for 10 h. The mixture was quenched with 20 mL H_2O, acidified with several drops of 4 N HCl solution, and extracted with 3 x 50 mL diethyl ether. The combined organic layers were washed with 30 mL saturated $NaHCO_3$ solution, 30 mL brine, then dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil was purified to 90% purity by flash chromatography (hexane: ethyl acetate = 48: 1) to afford 1.2 g (6 mmol) of material. Without further purification, this material was added to a suspension of palladium(II) chloride (0.1 g, 0.6 mmol), copper(I) chloride (0.6 g, 6 mmol), dimethylformamide (5 mL), and H_2O (0.6 mL) that had stirred under a balloon of oxygen for 1 h.[44] The mixture was stirred for 4 h then quenched with water and extracted with 3 x 20 mL diethyl ether. The combined organic layers were washed with 20 mL brine and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the resulting oil was purified by flash chromatography (hexane: ethyl acetate = 9: 1) to afford 0.6 g (10% yield from 4-penten-1-ol) of a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J = 8.1 Hz, 2 H); 7.18 (t, J = 7.2 Hz, 2 H); 7.10 (t, J = 7.2 Hz, 1 H); 5.58 (m, 1 H); 5.08 (m, 2 H); 4.47 (d, J = 11.9 Hz, 1 H); 4.18 (d, J = 11.9 Hz, 1 H); 3.61 (q, J = 7.3 Hz, 1 H); 2.13 (t, J = 6.5 Hz, 2 H); 1.83 (q, J = 7.0 Hz, 2 H); 1.61 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.5, 138.3, 128.3, 127.7, 127.6, 127.4, 117.4, 79.3, 70.0, 39.2, 29.9, 29.2. IR (neat): 3030, 2926, 1717, 1452, 1422, 1356, 1166, 1071, 1028, 993, 928, 736, 699. Anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.97; H, 8.40.

Conversion of Enones to Cyclopentanones. General Procedure A. $Cp_2Ti(PMe_3)_2$ (0.1 equiv), toluene (2-3 mL), PMe_3 (0.6 equiv), and enone (1.0 equiv, thoroughly dried by passage through a column of activated alumina) were added to a dry Schlenk tube in a glovebox under argon. The solution was cooled at -40°C for 20 min, then Ph_2SiH_2 (1.0 equiv, also thoroughly dried by passage through a column of activated alumina) was added. The flask was then sealed, removed from the glovebox, and placed in a -20°C bath to be stirred for 16-48 h. After this time, the solution was allowed to warm to room temperature. The toluene was removed *in vacuo* and acetone (10 mL) and 1 N HCl (1 mL) were added. The mixture was stirred for 1-4 h and then was diluted with 30 mL ether and 30 mL sat. NH_4Cl solution. The organic layer was washed with brine and dried over $MgSO_4$ to afford the crude product.

General Procedure B. $Cp_2Ti(PMe_3)_2$ (0.1 equiv), toluene (2-3 mL), PMe_3 (0.6 equiv), and enone (1.0 equiv, thoroughly dried by passage through a column of activated alumina) were added to a dry Schlenk tube in a glovebox under argon. The solution was cooled at -40°C for 20 min, then Ph_2SiH_2 (1.0 equiv, also thoroughly dried by passage through a column of activated alumina) was added. The flask was then sealed, removed from the glovebox, and placed in a -20°C bath to be stirred for 16-48 h. After this time, the solution was allowed to warm to room temperature. The toluene was removed *in vacuo* and the residue was put under an atmosphere of argon. THF (10 mL) and CH_2Cl_2 (10 mL) were added and the solution was cooled to 0°C. Trifluoroacetic acid (3 mL) and H_2O (0.3 mL) were added, and the reaction was stirred vigorously as the ice bath warmed to room temperature. After 16 h, saturated $NaHCO_3$ solution (30 mL) was added *slowly*, and after bubbling ceased, the reaction mixture was poured into a seperatory funnel containing 30 mL each of ethyl ether and H_2O. The aqueous layer was extracted with 30 mL portions of ethyl ether and ethyl

acetate, then the combined organic layers were washed with brine and dried over $MgSO_4$ to afford the crude product.

General Procedure C. $Cp_2Ti(PMe_3)_2$ (0.1 equiv), toluene (2-3 mL), PMe_3 (0.6 equiv), and enone (1.0 equiv, thoroughly dried by passage through a column of activated alumina) were added to a dry Schlenk tube in a glovebox under argon. The solution was cooled at -40°C for 20 min, then Ph_2SiH_2 (1.0 equiv, also thoroughly dried by passage through a column of activated alumina) was added. The flask was then sealed, removed from the glovebox, and placed in a -20°C bath to be stirred for 16-48 h. After this time, the solution was allowed to warm to room temperature. The toluene was removed *in vacuo* to afford the crude product.

General Procedure D. $Cp_2Ti(PMe_3)_2$ (0.1 equiv), toluene (2-3 mL), PMe_3 (0.6 equiv), and enone (1.0 equiv, thoroughly dried by passage through a column of activated alumina) were added to a dry Schlenk tube in a glovebox under argon. The solution was cooled at -40°C for 20 min, then Ph_2SiH_2 (1.0 equiv, also thoroughly dried by passage through a column of activated alumina) was added. The flask was then sealed, removed from the glovebox, and placed in a -20°C bath to be stirred for 16-48 h. After this time, the solution was allowed to warm to room temperature. The toluene was removed *in vacuo* and the residue was put under an atmosphere of argon. THF (5 mL) and then 1 N TBAF in THF (5 mL) were added and the reaction was stirred for 15 min. The THF was removed *in vacuo* and residue was taken up in ether and water (30 mL each). The organic layer was washed with brine and dried over $MgSO_4$ to afford the crude product.

***In situ* generation of the catalyst: General Procedure E.** Finely crushed Cp_2TiCl_2 (0.15 equiv) was added to a dry Schlenk flask under argon. The

flask was evacuated and backfilled three times with argon, then 2 mL toluene was added. The suspension was cooled to -78°C and 0.3 equiv *n*-BuLi added, then after 10 min, 1 equiv PMe_3 added. The red-colored mixture was stirred for 1 h at -78°C then for 1 h at 0°C, during which time the solution turned brown. The reaction mixture was then cannula filtered into a dry Schlenk tube containing 1 equiv of enone. The resulting red solution was cooled to -20°C, Ph_2SiH_2 was added, and the reaction was stirred at low temperature for 16-48 h. After this time, the solution was allowed to warm to room temperature. The toluene was removed *in vacuo* and acetone (10 mL) and 1 N HCl (1 mL) were added. The mixture was stirred for 1-4 h and then was diluted with 30 mL ether and 30 mL sat. NH_4Cl solution. The organic layer was washed with brine and dried over $MgSO_4$ to afford the crude product.

1,2-Dimethylcyclopentanol (Table 2, Entry 1).[48] Procedure A was used to convert 6-hepten-2-one (0.230 g, 2.34 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (pentane: ethyl ether = 4: 1) afforded 0.150 g (65% yield) of a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.8 - 1.3 (m, 7 H), 1.25 (s, 3 H), 1.13 (s, 1 H), 0.94 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 79.8, 43.8, 41.0, 32.1, 25.9, 20.8, 12.4. IR (neat): 3418, 2959, 2873, 1454, 1374, 1292, 1213, 1151, 1088, 1030, 916, 875, 841, 734.

1,2-Dimethyl-1-*n*-Propylcyclopentanone (Table 2, Entry 2).[49] Procedure A was used to convert 8-nonen-4-one (0.254 g, 1.8 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (ethyl ether: pentane = 1:6) afforded 0.170 g (67% yield) of the desired compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 - 1.25 (m, 11 H), 0.96 (t, J = 7.9 Hz, 3 H), 0.92 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 82.2, 42.9, 41.9, 38.3, 32.1, 21.0, 18.0, 14.8, 12.5. IR (neat): 3478, 2956, 2872, 1456, 1378, 942, 735.

9-Methyl-Bicyclo[4.3.0]nonan-1-ol (Table 2, Entry 3). Procedure A was used to convert 2-homoallylcyclohexanone (0.138 g, 0.9 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography afforded 0.10 g (72% yield) of a 9: 1 mixture of cyclized product and the carbonyl reduction product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) mixture: δ 2.1 - 1.0 (m, 15 H), 0.90 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.0, 47.1. 36.2, 33.7, 31.1, 29.6, 27.8, 25.0, 23.2, 12.8. IR (neat) mixture: 3443, 2928, 2856, 1448, 1120, 1076, 997, 952, 939. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.77; H, 11.73.

Diethyl-2-Methylcyclopentanol-4,4-Dicarboxylate (Table 2, Entry 4). Procedure B was used to convert diethyl-5-hexen-1-al-3,3-dicarboxylate (0.183 g, 0.75 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (pentane: ethyl ether = 7:3) afforded 0.121 g (66% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (m, 4 H), 4.08 (m, 1 H), 2.48 (m, 1 H), 2.45 (dd, J = 14.9 Hz, J = 16.1 Hz, 1 H), 2.34 (dd, J = 4.4 Hz, J = 14.9 Hz, 1 H), 2.03 (m, 1 H), 2.01 (s, 1 H). 1.98 (m, 1 H), 1.24 (td, J = 7.1 Hz, J = 2.5 Hz, 6 H), 1.06 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (75 MHz, C_6D_6): δ 173.7, 173.0, 75.8, 61.9, 61.6, 59.5, 44.1, 40.7, 39.9, 14.34, 14.30, 13.6. IR (neat): 3534, 2979, 1731, 1446, 1367, 1259, 1181, 1146, 1096, 1038, 961, 862, 756. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 59.23; H, 8.19.

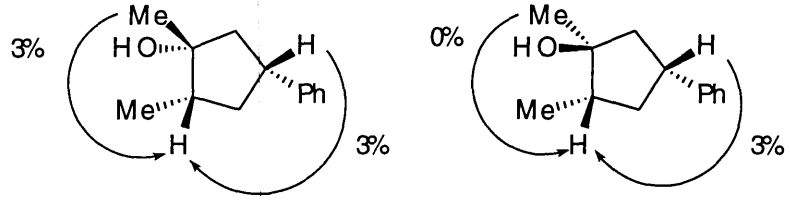
Diethyl-1,2-Dimethylcyclopentanol-4,4-Dicarboxylate (Table 2, Entry 5). Procedure B was used to convert diethyl-6-hepten-2-one-4,4-dicarboxylate (0.232 g, 0.75 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (hexane: ethyl acetate = 9: 1) afforded 0.161 g (69%

yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (m, 4 H), 2.54 (dd, *J* = 8.0 Hz, *J* = 13.8 Hz, 1 H), 2.50 (d, *J* = 14.8 Hz, 1 H), 2.21 (d, *J* = 14.8 Hz, 1 H), 2.11 (s, 1 H), 2.03 (dd, *J* = 12.2 Hz, 1 H), 1.82 (m, 1 H), 1.259 (m, 9 H), 0.97 (d, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 172.6, 79.5, 61.8, 61.5, 57.1, 48.9, 43.9, 40.5, 24.5, 14.0, 13.9, 11.4. IR (neat): 3533, 2976, 1731, 1447, 1368, 1259, 1153, 1061, 930, 867. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.58; H, 8.38.

1,2,4,4-Tetramethylcyclopentanol (Table 2, Entry 6).[50] Procedure A was used to convert 4,4-dimethyl-6-hepten-2-one (0.140 g, 1.0 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (pentane: ethyl ether = 4: 1) afforded 85 mg (61% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (m, 1 H), 1.7 - 1.4 (m, 4 H), 1.22 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 1 H), 1.00 (s, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.1, 56.6, 48.5, 43.4, 35.2, 31.9, 31.8, 26.8, 11.8. IR (neat): 3472, 2953, 2866, 2361, 1456, 1372, 1303, 1236, 1210, 1079, 1009, 933, 910, 847.

1,2-Dimethyl-4-Phenylcyclopentanol (Table 2, Entry 7). Procedure A was used to convert 4-phenyl-6-hepten-2-one (0.188 g, 1.0 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (hexane: ethyl acetate = 5.7: 1) afforded 0.117 g (62% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 4 H), 7.15 (m, 1 H), 3.09 (m, 1H), 2.30 (dd, *J* = 10.2 Hz, *J* = 14.1 Hz, 1 H), 2.12 (m, 1 H), 1.90 (dd, *J* = 7.1 Hz, *J* = 15.0 Hz, 1 H), 1.78 (m, 1 H), 1.69 (m, 1 H), 1.32 (s, 3 H), 1.20 (s, 1 H), 1.01 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 128.3, 127.3, 125.7, 79.6, 49.7, 45.2, 42.7, 42.2, 27.3, 12.1. IR (neat): 3576, 3461, 2958, 2931, 2871, 1945, 1871, 1804, 1602, 1493, 1455, 1373, 1121, 1031, 922, 847, 759, 700. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.84; H, 9.70. A nuclear Overhauser enhancement study was undertaken to

determine the relative configuration of the two isomers. For the major isomer, irradiation of the C-3 hydrogen at δ 3.09 gave a 3% enhancement at the C-4 hydrogen, and irradiation of the C-1 methyl at δ 1.32 gave a 3% enhancement at the C-4 hydrogen. For the minor isomer, irradiation of the C-3 hydrogen at δ 3.36 also gave a 3% enhancement at the C-4 hydrogen, while irradiation of the C-1 methyl at δ 1.01 gave no enhancement at the C-4 hydrogen. Based on these observations, the configuration of the isomers were assigned as shown:

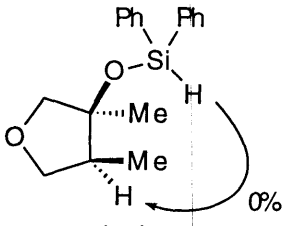


1,2-Dimethyl-4-Phenyl-4-Azacyclopentanol (Table 2, Entry 8).

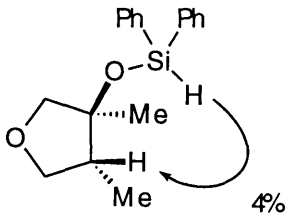
Procedure A was used to convert *N*-allyl-*N*-acetonyl aniline (0.177 g, 9.3 mmol) to the mixture of desired products. Purification by Kugelrohr distillation followed by separation on a chromatatron (hexane; ethyl acetate = 9: 1) afforded 61 mg of isomer A and 69 mg of isomer B (36% and 40% yields respectively) as colorless oils which turn to a blue color over time if not stored at low temperature. ^{1}H NMR (300 MHz, $CDCl_3$): Isomer A: δ 7.21 (t, *J* = 8.8 Hz, 2 H), 6.65 (t, *J* = 8.3 Hz, 1 H), 6.50 (d, *J* = 8.8 Hz, 2 H), 3.42 (dd, *J* = 8.7 Hz, 1 H), 3.29 (dd, *J* = 10.3 Hz, *J* = 17.1 Hz, 1 H), 3.07 (dd, *J* = 9.5 Hz, 1 H), 2.09 (m, 1 H), 1.68 (s, 1 H), 1.34 (s, 3 H), 1.05 (d, *J* = 6.7 Hz, 3 H). Isomer B: δ 7.22 (t, *J* = 7.7 Hz, 2 H), 6.66 (t, *J* = 7.3 Hz, 1 H), 6.50 (d, *J* = 7.8 Hz, 2 H), 3.63 (dd, *J* = 7.2 Hz, *J* = 9.3 Hz, 1 H), 3.28 (dd, *J* = 9.8 Hz, *J* = 21.0 Hz, 2 H), 2.94 (dd, *J* = 5.5 Hz, *J* = 9.3 Hz, 1 H), 2.22 (m, 1 H), 1.94 (s, 1 H), 1.29 (s, 3 H), 1.0 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): Isomer A: δ 129.1, 115.8, 111.4, 102.2, 77.4, 61.6, 53.7, 42.2, 23.0, 10.1. Isomer B: δ 129.1, 115.8, 111.3, 102.2, 78.6, 59.9, 54.0, 43.4, 21.3, 14.5. IR (neat): Isomer A: 3433, 2965, 2833, 1919, 1810, 1599, 1509, 1472,

1386, 1194, 1120, 938, 873, 750, 691. Isomer B: 3396, 2967, 2841, 1912, 1711, 1662, 1599, 1505, 1481, 1372, 1184, 1141, 999, 747, 692. Anal. Calcd for $C_{12}H_{17}NO$ (A): C, 75.35; H, 8.96. Found: C, 75.32; H, 8.86.

1,2-Dimethyl-4-Oxacyclopenanol-Diphenylsilyl Ether (Table 2, Entry 9). Procedure D was used to convert allyl acetonyl ether (0.103 g, 0.9 mmol) to the desired product. Purification by Kugelrohr distillation afforded 0.210 g (77% yield) of a 3:2 mixture of the desired compounds as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) mixture: Isomer A: δ 7.62 (m, 4 H), 7.39 (m, 6 H), 5.55 (s, 1 H), 4.03 (dd, J = 7.8 Hz, J = 15.8 Hz, 2 H), 3.62 (dd, J = 10.2 Hz, J = 20.0 Hz, 2 H), 2.01 (m, 1 H), 1.34 (s, 3 H), 1.03 (d, J = 6.9, 3 H). Isomer B: δ 7.62 (m, 4 H), 7.39 (m, 6 H), 5.55 (s, 1 H), 4.17 (t, J = 8.1 Hz, 1 H), 3.88 (d, J = 9.0 Hz, 1 H), 3.66 (d, J = 10.4 Hz, 1 H), 3.43 (t, J = 7.8 Hz, 1 H), 2.32 (m, 1 H), 1.33 (s, 3 H), 0.92 (d, J = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) mixture: δ 134.4 (2), 130.0, 130.1, 127.9 (4), 83.6, 82.1, 79.3, 78.3, 74.9, 74.2, 49.7, 44.8, 22.3, 20.6, 14.2, 9.0. IR (neat) mixture: 3135, 3068, 3049, 3000, 2969, 2930, 2867, 2123, 1959, 1889, 1823, 1589, 1455, 1428, 1383, 1324, 1241, 1154, 1112, 1058, 1036, 1012, 926, 890, 824, 734, 699. Anal. Calcd for $C_{18}H_{22}O_2Si$ (mixture): C, 72.44; H, 7.43. Found: C, 72.68; H, 7.55. A nuclear Overhauser enhancement study was undertaken to determine the relative configurations of the two isomers observed. For the major isomer, irradiation of the Si hydrogen at δ 5.55 gave no enhancement at the C-2 hydrogen, while for the minor isomer, irradiation of the Si hydrogen at δ 5.55 gave a 4% enhancement at the C-2 hydrogen. Based on this observation, the relative configurations of the two isomers were assigned as shown:



major isomer



minor isomer

1,2-Dimethyl-1-Hydroxy-2,3-Dihydroindene (Table 2, Entry 10a). Procedure B was used to convert *ortho*-allylacetophenone (0.160 g, 1.0 mmol) to the desired product. Purification by flash chromatography (ethyl acetate: hexane = 1:4) followed by Kugelrohr distillation afforded 0.144 g (89% yield) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (m, 1 H), 7.24 (m, 3 H), 2.96 (dd, J = 7.2 Hz, J = 15.6 Hz, 1 H), 2.66 (dd, J = 9.0 Hz, J = 15.6 Hz, 1 H), 2.25 (m, 1 H), 1.56 (s, 3 H), 1.38 (s, 1 H), 1.16 (d, J = 7.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 142.6, 128.3, 126.7, 124.9, 122.6, 80.7, 45.0, 37.9, 25.1, 12.9. IR (neat): 3422, 3068, 2967, 1913, 1707, 1606, 1477, 1375, 1290. 1215, 1183, 1076, 912, 841, 761, cm^{-1}. Anal. Calcd for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.19; H, 8.66.

1,2-Dimethylindene (Table 2, Entry 10b).[51] Procedure A was used to convert *ortho*-allylacetophenone (0.146 g, 0.91 mmol) to the desired product. Purification by Kugelrohr distillation followed by flash chromatography (hexane) afforded 93 mg (71% yield) of the desired compound as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 8.3 Hz, 1 H), 7.23 (m, 2 H), 7.10 (t, J = 6.5 Hz, 1 H), 3.25 (s, 2 H), 2.05 (s, 3 H), 2.02 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 142.3, 137.9, 132.4, 126.0, 123.6, 123.0, 117.9, 42.4, 13.8, 10.1. IR (neat): 3066, 3042, 2911, 1933, 1897, 1782, 1636, 1607, 1467, 1458, 1395, 1226, 1205, 1015, 757, 717. Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.49; H, 8.64.

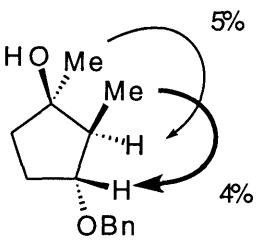
Ethyl-1,2-Dimethylcyclopentanol-5-carboxylate (Table 2, Entry 11). Procedure B was used to convert ethyl-6-hepten-2-one-3-carboxylate (0.166 g, 0.9 mmol) to the title compound. Purification by Kugelrohr distillation followed by flash chromatography (pentane: ethyl acetate = 3: 1) afforded 0.132 g (79% yield) of a

colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14 (qd, J = 7.0 Hz, J = 2.1 Hz, 2 H); 2.83 (t, J = 6.5 Hz, 1 H); 1.91 (m, 4 H); 1.66 (s, 1 H); 1.21 (m, 1 H); 1.28 (t, J = 7.1 Hz, 3 H); 1.21 (s, 3 H); 0.96 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 81.6, 60.3, 55.8, 43.1, 30.9, 24.9, 23.7, 14.3, 13.0. IR (neat): 3508, 2966, 2906, 2875, 1784, 1716, 1455, 1373, 1342, 1299, 1253, 1188, 1096, 1039, 917, 857. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.36; H, 9.86.

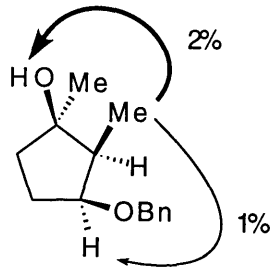
5-Benzyl-1,2-Dimethylcyclopentanol (Table 2, Entry 12). Procedure A was used to convert 3-benzyl-6-hepten-2-one (0.153 g, 0.76 mmol) to the title compound. Purification by Kugelrohr distillation followed by flash chromatography (hexane; ethyl acetate = 12: 1) afforded 0.120 g (77% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2 H); 7.24 (m, 3 H); 2.93 (dd, J = 3.4 Hz, J = 12.6 Hz, 1 H); 2.23 (t, J = 11.7 Hz, 1 H); 2.15 (m, 1 H); 1.75 (m, 3 H); 1.23 (s, 3 H); 1.22 (m, 2 H); 1.19 (s, 1 H); 0.96 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 128.9, 128.3, 125.7, 81.1, 51.4, 42.9, 37.8, 30.3, 27.6, 23.4, 14.0. IR (neat): 3449, 3028, 2956, 2871, 1583, 1495, 1452, 1372, 910, 698. Anal. Calcd for $C_{14}H_{20}O$: C, 82.29; H, 9.87. Found: C, 82.50; H, 9.82.

3-Benzyloxy-1,2-Dimethylcyclopentanol (1,2-*cis*-2,3-*trans* and 1,2-*cis*-2,3-*cis*) (Table 2, Entry 13). Procedure B was used to convert 5-benzyloxy-6-hepten-2-one (99 mg, 0.45 mmol) to the title compound. Purification by Kugelrohr distillation followed by flash chromatography (hexane: ethyl acetate = 9:1 (200 mL), 2.5:1 (100 mL)) afforded 38 mg 1,2-*cis*-2,3-*trans* title compound and 14 mg 1,2-*cis*-2,3-*trans* title compound (52% combined yield) as colorless oils. **1,2-*cis*-2,3-*trans*:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5 H); 4.58 (d, J = 11.7 Hz, 1 H); 4.45 (d, J = 11.7 Hz, 1 H); 3.72 (m, 1 H); 2.13 (m, 1 H); 1.89 (m, 1 H); 1.70 (m, 3 H), 1.27 (s, 3 H), 1.10 (s 1 H), 1.04 (d, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 128.3, 127.7,

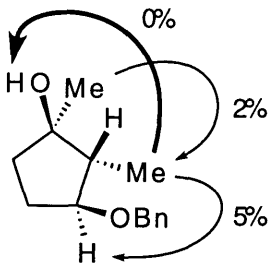
127.4, 86.2, 79.1, 71.7, 50.1, 38.5, 28.3, 26.7, 10.6. IR (neat): 3528, 2965, 1453, 1406, 1061, 1028, 734, 696. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.16. Found: C, 76.04; H, 9.30. **1,2-*cis*-2,3-*cis*.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 5 H); 4.64 (d, J = 12.2 Hz, 1 H); 4.38 (d, J = 12.2 Hz, 1 H); 3.90 (t, J = 4.9 Hz, 1 H); 3.19 (s, 1 H); 2.01 (m, 2 H); 1.78 (m, 2 H); 1.60 (m, 1 H); 1.23 (s, 3 H); 1.10 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 128.3, 127.5, 127.3, 84.3, 79.6, 70.8, 48.2, 40.0, 28.1, 24.7, 7.5. IR (neat): 3448, 2962, 2871, 1453, 1207, 1091, 1027, 917, 734, 697. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.16. Found: C, 76.30; H, 9.28. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the three isomers observed. For the 1,2-*cis*-2,3-*trans* isomer (major isomer), irradiation of the C-1 methyl at δ 1.27 gave a 5% enhancement at the C-2 hydrogen, and irradiation of the C-2 methyl at δ 1.04 gave a 4% enhancement at the C-3 hydrogen. For the 1,2-*cis*-2,3-*cis* isomer (minor isomer), irradiation of the C-2 methyl at δ 1.10 gave a 2% enhancement at the C-1 hydroxyl, but only a 1% enhancement of the C-3 hydrogen. For the 1,2-*trans*-2,3-*cis* isomer (not isolated, but observed when reaction run at -20°C), irradiation of the C-1 methyl at δ 1.21 gave a 2% enhancement of the C-2 methyl, but only a 1% enhancement at the C-2 hydrogen. Irradiation of the C-1 methyl at δ 0.87 gave a 5% enhancement at the C-3 hydrogen and no enhancement at the C-1 hydroxyl. Based on these observations, the configurations of the three isomers were assigned as shown:



1,2-*cis*-2,3-*trans*



1,2-*cis*-2,3-*trans*



1,2-*trans*-2,3-*trans*

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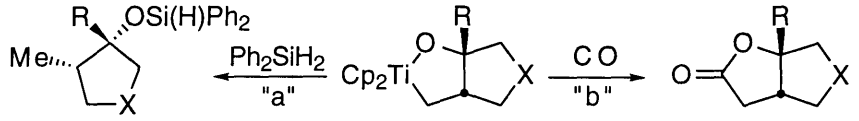
CHAPTER 2

DIASTEREOSELECTIVE SYNTHESIS OF γ-BUTYROLACTONES FROM ENONES MEDIATED BY TITANOCENE CATALYSTS

Introduction

The catalytic reductive cyclization described in Chapter 1 demonstrated that the oxametallacycles **1**, first described by Whitby, can be used as intermediates for catalytic organic transformations — in particular, the reductive cyclization of enones (Scheme 1, pathway "a").[1-3] We next became interested in using oxametallacycle **1** as an intermediate for the synthesis of more highly functionalized products, in particular the reaction of the metallacycle with carbon monoxide to form lactone **3** (Scheme 1, pathway "b").

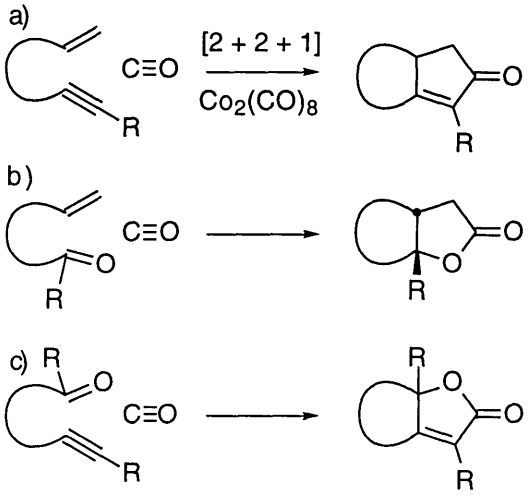
Scheme 1



2 **1** **3**

The growing interest in the development of organic reactions mediated or catalyzed by organotransition metals stems from their ability to assemble complex molecules from simple starting materials[4] in a convergent and atom-economical manner.[5] One reaction that exemplifies this concept is the Pauson-Khand reaction, in which an alkyne, an alkene, and carbon monoxide are condensed in a formal [2+2+1] cycloaddition to form cyclopentenones using $Co_2(CO)_8$ (Scheme 2a).[6] This reaction has been used extensively by organic chemists in the synthesis of a variety of natural products.[7] We envisioned a heteroatom variant of the Pauson-Khand reaction in which either the alkyne can be replaced by a carbonyl to result in the formation of γ-butyrolactones (Scheme 2b), or the alkene can be replaced by a carbonyl to result in the formation of fused butenolides (Scheme 2c).

Scheme 2

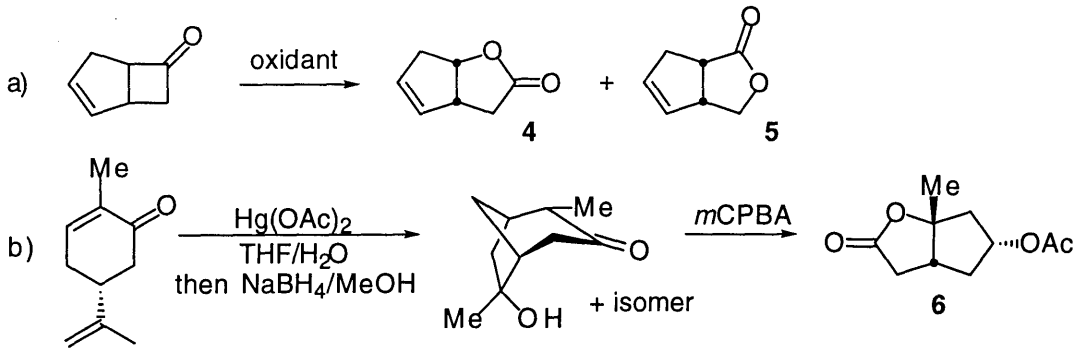


The biological importance of γ-butyrolactones and their role as integral substructures in numerous natural products[8] have made the γ-butyrolactone moiety a popular synthetic target. There have been many methods developed for the synthesis of γ-butyrolactones, and two extensive recent reviews have discussed these methods.[9,10] Most of the methodologies developed fit into four general categories, and examples from each category are presented below.

Lactones can be synthesized by the reduction or oxidation of an existing ring system, for example Baeyer Villiger oxidation,[11] oxidation of lactols, or reduction of dicarboxylic anhydrides.[12] Scheme 3a shows an example of the Baeyer-Villiger oxidation of a bicyclic cyclobutanone to γ-butyrolactones **4** and **5**. In most cases γ-butyrolactone **4** is formed, but varying amounts of **5** are often observed.[13] There have been a number of enzymatic systems that have been developed which carry out this transformation with high ee in an enantiodivergent manner, but a 1 to 1 mixture of **4** and **5** is produced.[14] Scheme 3b shows an interesting example of the synthesis of a γ-butyrolactone from (*R*)-(—)-Carvone.[15] The key step is a Baeyer-Villiger Oxidation followed by

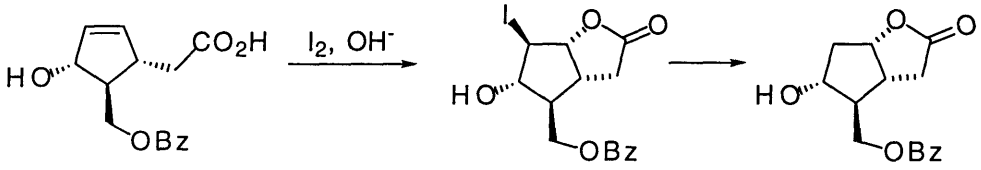
a rearrangement to produce lactone **6**. This intermediate is used in the total synthesis of (—)-Hirsutene.

Scheme 3



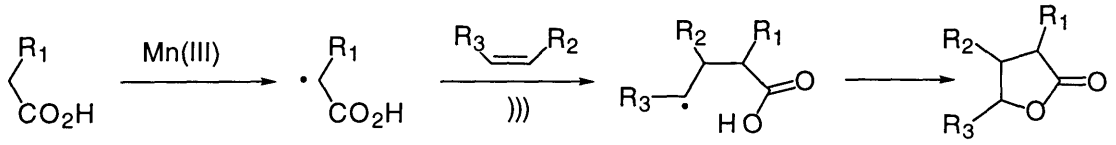
A second general strategy for γ-butyrolactone synthesis is by the closure of a single ring, for example by radical methods,[16] acid catalysis,[17] or iodolactonization.[18] Scheme 4 shows an example of an iodolactonization utilized by Corey in the total synthesis of prostaglandins $F_{2\alpha}$ and E_2.[19]

Scheme 4



Annulation strategies that unite two moieties to form a single ring make up a third class of methods for lactone syntheis.[20] Many of these reactions are mechanistically similar to those discussed above for the closure of a single ring. For example, the lactonization of olefins promoted by Mn(III) proceeds *via* a radical cyclization as shown in Scheme 5.[21]

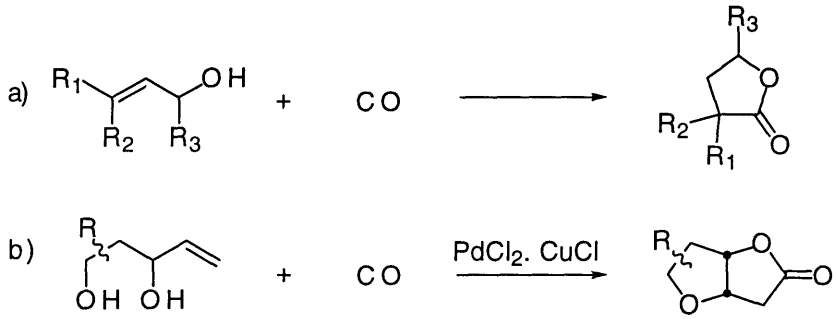
Scheme 5



Another notable strategy is the cyclocarbonylation of allylic alcohols using late transition metal catalysts, including complexes of palladium, nickel, and rhodium.[22] The general reaction is shown in Scheme 6a.[23] An interesting

use of a related strategy for the construction of lactones similar to those generated by our methodology is shown in Scheme 6b. Here, *cis*-3-hydroxytetrahydrofuranacetic acid lactones are produced by the intramolecular palladium-catalyzed oxycarbonylation of 4-pentene-1,3-diols.[24]

Scheme 6

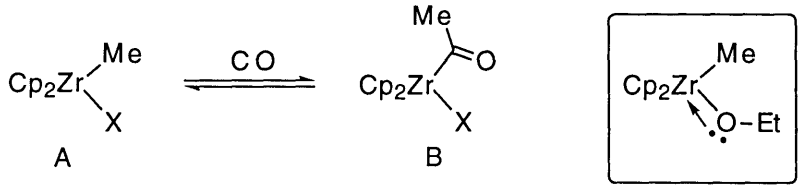


The general methods outlined above have all proven to be extremely useful in organic synthesis, but in most cases, only a single ring or a single carbon-carbon bond is formed in the reaction. Similar to the intramolecular Pauson-Khand reaction, the benefit of our proposed method is its convergence; two rings and two carbon-carbon bonds are constructed in a single step, and its versatility as a three-component annulation strategy.

Precedence for the "Hetero Pauson-Khand" Reaction. There is some precedence for the carbonylation of the titanium-carbon bond of metallacycle **1**. In related all-carbon metallacycles, insertion of CO and isonitriles into the Ti-C bonds is a facile process; there are many examples of enyne cyclocarbonylations using early transition metals in a Pauson-Khand type of reaction.[25-27] Studies conducted by Caulton[28] on the carbonylation (at 1 atm) of the related $Cp_2Zr(Me)X$ system show that insertion of CO into the Zr-C bond is heavily dependent on the nature of the ligand X. Facility of carbonylation is found to decrease in the series: Me > Cl > OEt, with no carbonylation observed for $Cp_2Zr(Me)OEt$. These results were deemed to reflect the ability of the lone pairs on the alkoxide and chloride to π-donate into

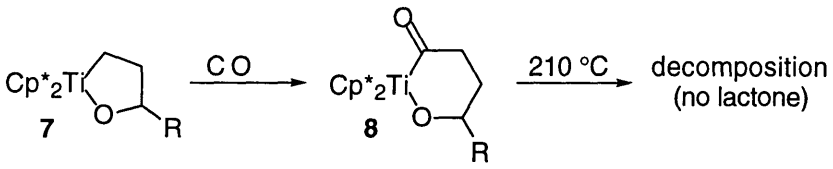
the vacant metal orbital, rendering the complex coordinatively saturated (18 e$^-$) and thus hindering the carbonylation reaction (Scheme 7). This study suggests that the carbonylation of early transition metal oxametallacycles would be difficult. The metallacycles in our system may carbonylate more readily since the orbital overlap between the oxygen lone pair and the titanium LUMO is unefficient in cyclic systems. For example, Takaya[29] showed that carbonylation does occur in the more electron-rich, and hence less oxophilic, Cp^*_2Ti oxametallacycle systems, **7** (Scheme 8). The CO inserts into the Ti-C bond to form carbonylated metallacycles, **8**, but these metallacycles do not undergo thermally-induced reductive elimination to form γ-butyrolactones; instead they decompose at elevated temperatures (210 °C). Reductive elimination of oxametallacyclic systems may be more difficult than in all carbon metallacycles due to the strength of titanium-oxygen bonds.[30]

Scheme 7



B/A: Me > Cl > OEt

Scheme 8

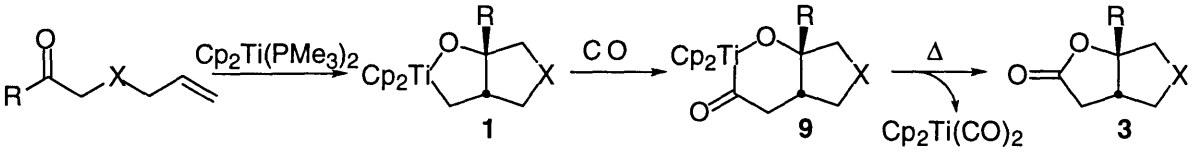


Results and Discussion

We[31] and Crowe[32] have found that carbonylation of the titanacycle **1** also occurs, with CO inserting into the Ti-C bond to form carbonylated metallacycle **9** (Scheme 9). Reductive elimination is induced thermally (70 °C), resulting in the formation of γ-butyrolactone **3** and titanocene dicarbonyl as the coproduct. It

should be noted that reductive elimination also occurs when metallacycle **1** is exposed to air, but the resulting lactones are formed in significantly lower yields.[32]

Scheme 9



Crystal Structure of Carbonylated Intermediate 9: As shown in Scheme 9, the mechanism of the "hetero Pauson-Khand" reaction is postulated to go through the carbonylated metallacycle **6**. In most cases we have found that these carbonylated metallacycles slowly undergo reductive elimination at room temperature, but if R = H, this intermediate (**9a**) is isolable as purple prismatic crystals suitable for x-ray crystallographic analysis. The crystals were grown and isolated under argon by slow evaporation of a THF solution at -30 °C. Figure 1 shows the crystal structure, and selected bond lengths and bond angles are shown in Table 1. The complex crystallizes in the space group P1 with a triclinic unit cell. The Ti—C(11) bond length is 2.219(7) Å, and the Ti—O(1) bond length is 1.846(4) Å which are typical for Ti—C and Ti—O single bonds. The Ti-O(2) distance of 3.116(5) Å and the O1—C11—Ti bond angle of 127.6 ° indicate that the acyl is bound to the titanium in an η^1 fashion. Crowe has also reported an x-ray structure for a similar carbonylated metallacycle.[32]

Synthetic Results: Table 2 shows our results applying the "hetero Pauson-Khand" reaction. The reactions were carried out, in most cases, under the conditions shown in Scheme 10 using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$. Several substrates (Table 2, entries 2, 3, and 10) were also transformed to the corresponding lactone using a method in which the titanocene reagent is generated *in situ* from the commercially available,

inexpensive, air- and moisture-stable titanocene dichloride, along with *n*-BuLi, and PMe_3. This procedure is analogous to the one developed for the catalytic reductive cyclization described in Chapter 1.[33] Since the hetero Pauson-Khand reaction uses a stoichiometric amount of $Cp_2Ti(PMe_3)_2$, which is a pyrophoric, air- and moisture-sensitive complex that must be synthesized, stored, and handled in a glovebox under argon, the *in situ* method is particularly convenient.

Table 1: Selected bond lengths [Å] and angles[°] for **9a**:

Bond Distance, Å		Angle, deg	
Ti—C11	2.219(7)	O1—Ti—C11	86.1(2)
Ti—O1	1.846(4)	O2—C11—Ti	127.6(5)
Ti—O2	3.116(5)	Ti—O1—C14	136.3(4)
C11—O2	1.219(8)	Ti—C11—C12	116.8(5)

Figure 1. Crystal structure of **9a**.

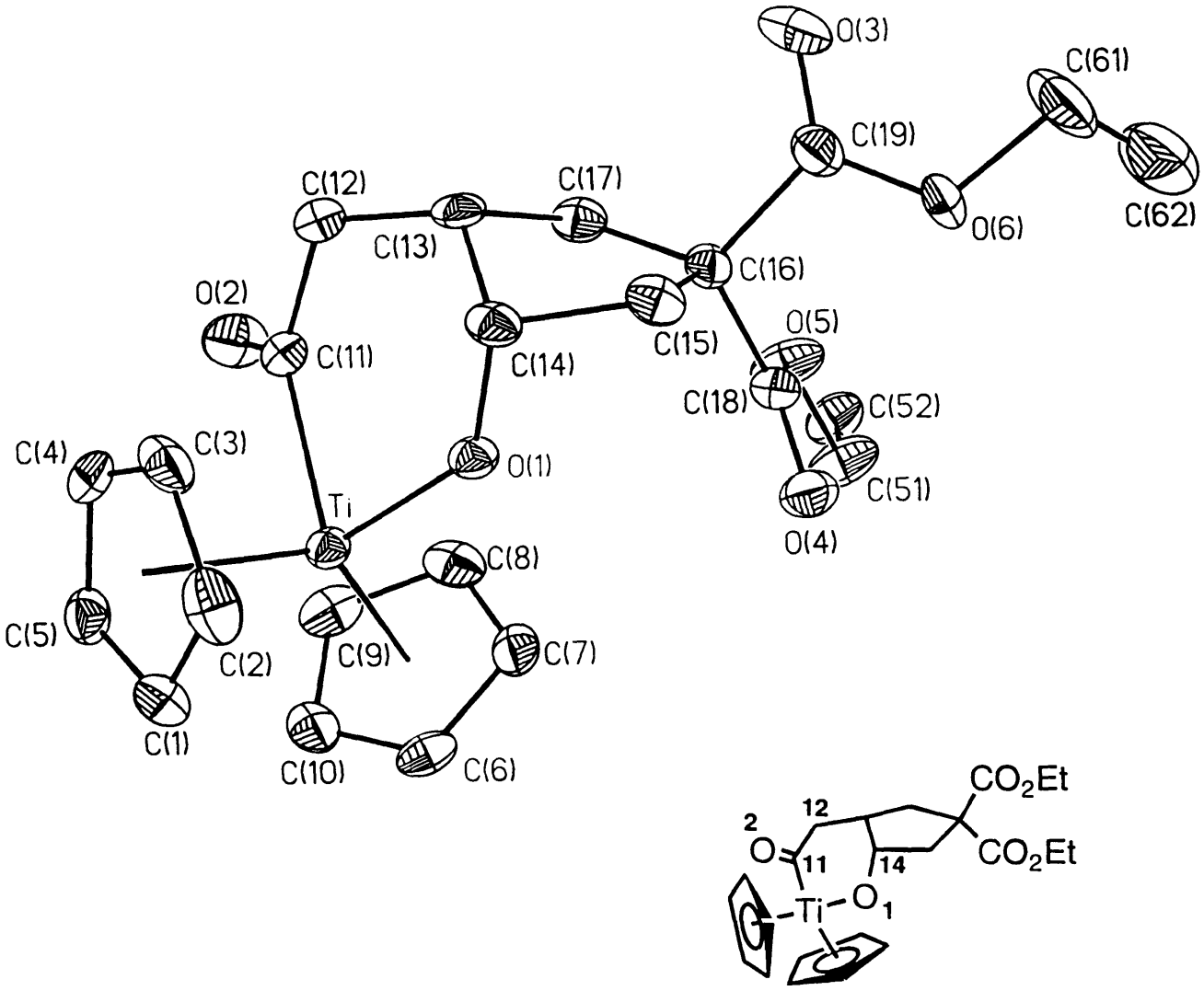
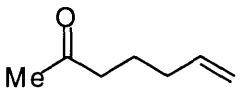
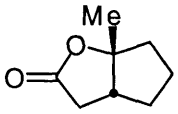
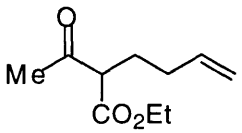
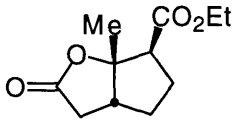
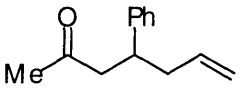
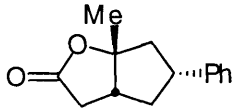
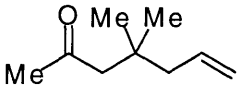
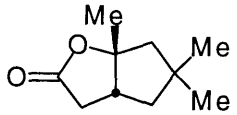
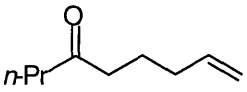
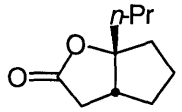
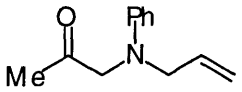
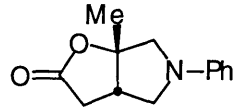
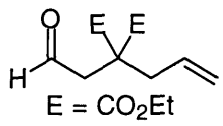
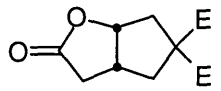
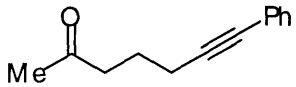
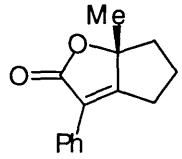
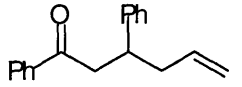
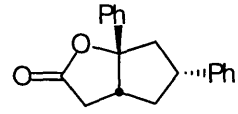
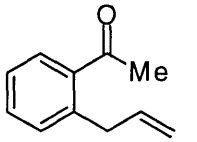
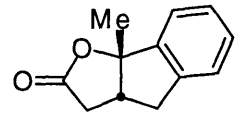
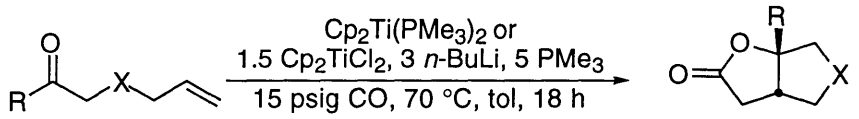


Table 2: Results of the "Hetero-Pauson-Khand" Reaction.

Entry	Substrate	Product[a]	Isolated Yield (%)[b, c]
1			65
2			90 (80)
3			92 (81)
4			85
5			95
6			80
7			61
8[d]			28
9[e]			54 [81][f]
10			95 (98)

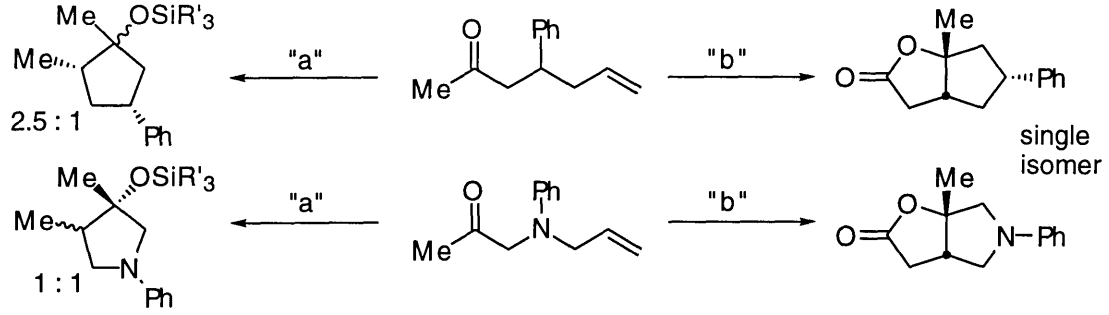
[a] Reaction conditions are with 1.1 eq $Cp_2Ti(PMe_3)_2$ at 15 psig CO and 70 °C for 18 h, unless otherwise noted. [b] Isolated yields of products > 95% purity as determined by ^1H NMR, GC, and are analytically pure. Yields are an average of 2 or more runs. [c] Yields in parentheses are those obtained from the *in situ* generation of the titanium reagent from 1.5 eq Cp_2TiCl_2, 3 eq *n*-BuLi, and 5 eq PMe_3. [d] Reaction run at 20 psig CO at 85 °C. [e] Reaction run at 1 atm CO at 90 °C. [f] Yield in brackets obtained by reaction of the substrate with 1.1 equiv $Cp_2Ti(CO)_2$ at 90 °C under argon.

Scheme 10



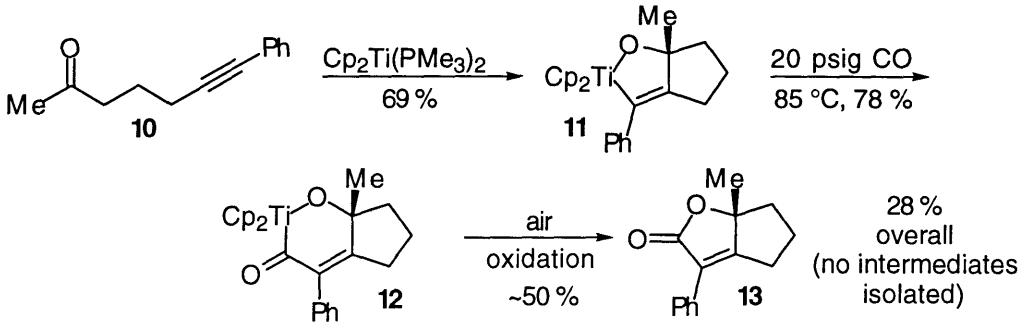
In the hetero Pauson-Khand reaction reported here, the γ-butyrolactones are formed with complete diastereoselectivity. This is in contrast to the results obtained in the previous work on the catalytic reductive cyclization of enones to cyclopentanols,[1-3] and to the recent report by Crowe on lactone synthesis.[32] For example, under the standard conditions for the catalytic reductive cyclization reaction (-20 °C), cyclopentanols derived from substrates with substituents β to the carbonyl give a 2.5 : 1 ratio of product cyclopentanols, and reactions of substrates with heteroatoms in the backbone are essentially nonselective (see Scheme 11). This marked difference in diastereoselectivity can be explained by noting that the formation of metallacycle **1** from enone and $Cp_2Ti(PMe_3)_2$ is a reversible process (see Chapter 1). The catalytic reductive cyclization (pathway "a") is run at low temperature (-20 °C), so the selectivities are under kinetic control. These conditions prevent the metallacycle from equilibrating to the thermodynamically favored isomer. However, the hetero Pauson-Khand reaction (pathway "b") is carried out at 70 °C, allowing complete conversion to a single isomer of metallacycle **1**. It should be noted that Crowe's method for the synthesis of γ-butyrolactones is run at room temperature, and his resulting diastereoselectivities are low. For example, a substrate with a substitutent in the β-position is transformed to the lactone in a diasteromeric ratio of 1.5 : 1.[3]

Scheme 11



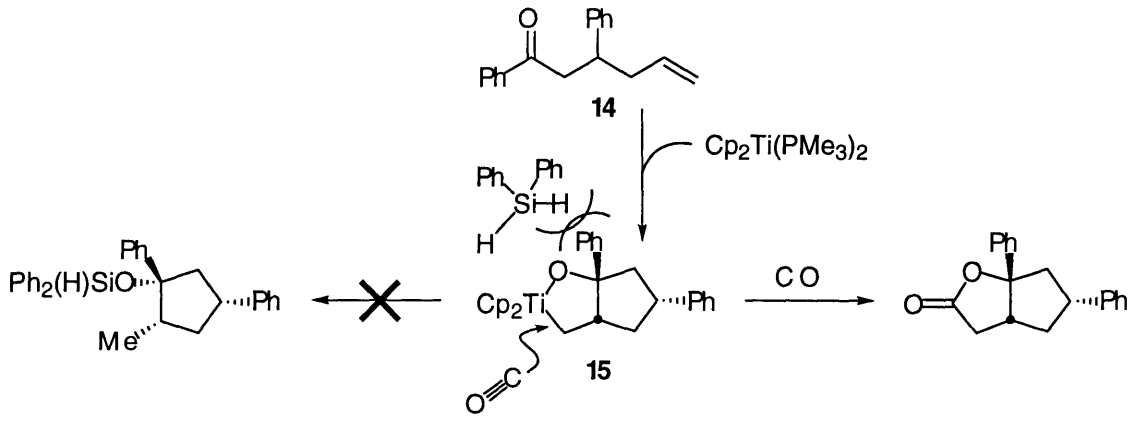
The hetero Pauson-Khand cyclization of the ynone (Table 2, entry 8) is of particular interest, since the insertion of CO into the hindered Ti-C(sp^2) bond has not been demonstrated in previous studies (Scheme 12).[34] For this substrate, slightly higher pressures (20 psig) and temperatures (85 °C) are used. Under these conditions, reductive elimination does not occur thermally; instead, reductive elimination is induced by exposure to air during chromatography and a low yield is obtained. We do not fully understand why ynones are problematic substrates for this reaction. The low yield partially stems from the inability of the carbonylated metallacycle to undergo thermally induced reductive elimination, since it has been shown that reductive elimination induced by air oxidation proceeds with significantly lower yields in the enone cases.[32] In addition, Whitby has shown that the formation of metallacycles from ynones proceeds with a lower yield than in the enone cases (60 % isolated yield for the methyl substituted alkyne compared to 76-83 % for metallacycles from enones, see Chapter 1).[35] We have conducted reactions in an NMR tube with an internal standard that show that ynone **10** reacts to form metallacycle **11** in 69 % yield. The carbonylation of **11** to form metallacycle **12** proceeds with 78 % yield from metallacycle **11** (54 % overall). The overall yield for the reaction to form butenolide **13** is only 28 %, which suggests that the air-induced reductive elimination proceeds with only a 50 % yield, but the other steps also contribute to the overall poor yield.

Scheme 12



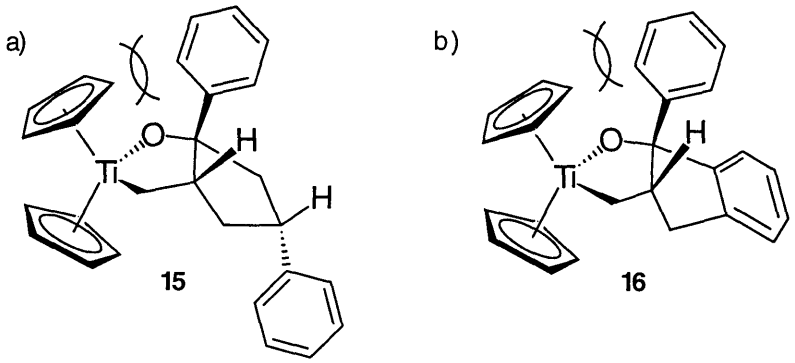
We note that the phenyl ketone **14** (Table 2, entry 9) is not a viable substrate for our previously reported catalytic reductive cyclization reaction, presumably due to the large phenyl group hindering the approach of the silane to the Ti—O bond of metallacycle **15**.[2] Since insertion in the hetero Pauson-Khand reaction occurs at the Ti—C bond of the intermediate metallacycle, this substrate is smoothly converted to the corresponding γ-butyrolactone (Scheme 13). The conditions employed are slightly different than the standard ones shown in Scheme 6 in that only one atmosphere of CO is used at 90 °C, and only a 54 % yield is obtained. If the standard conditions are used (15 psig CO at 70 °C) no lactone is formed. We found that this substrate is converted to the lactone in significantly higher yield (81 %) if titanocene dicarbonyl is used as the reagent under an atmosphere of argon rather than $Cp_2Ti(PMe_3)_2$ and CO.

Scheme 13



We speculate that enone **14** does not cleanly form metallacycle **15** (Scheme 13), and that the low yield of the lactone when $Cp_2Ti(PMe_3)_2$ is utilized as the reagent reflects the yield of the metallacycle. Indeed, in an experiment run in an NMR tube showed that the metallacycle is only formed in approximately 58 % yield versus an internal standard. We believe that a lower pressure of CO is required because the formation of the metallacycle is reversible;[2,35] the higher pressure of CO used in the standard conditions causes retrocyclization of the relatively unstable metallacycle. The instability of metallacycle **15** may be due to steric interactions between the large phenyl ketone substituent and the cyclopentadienyl rings on the titanium (see Figure 2). Note that in Chapter 3 *o*-allyl benzophenone, which also has a large phenyl ketone substitutent, is described as being a particularly good substrate for cyclization by titanocene complexes. In addition to the destabilizing phenyl ketone substituent, however, *o*-allyl benzophenone also has a phenyl ring fused to the backbone of the substrate, which we believe enhances the cyclization of enones by forcing the two reactive unsaturated moieties into close proximity (see Chapter 1). The metallacycle that results from *o*-allyl benzophenone, **16**, is shown in Figure 2b. Metallacycle **15** does not have this additional structural attribute to counterbalance the destabilizing effect of the phenyl ketone substituent, so the metallacycle is unstable.

Figure 2



The phenyl ketone substrate **14** also has the ability to react with titanocene dicarbonyl without added carbon monoxide in better yield than with the $Cp_2Ti(PMe_3)_2$ system. Most of the other enones in Table 2 do not react with titanocene dicarbonyl, so a full equivalent of $Cp_2Ti(PMe_3)_2$ is necessary to carry out the cyclocarbonylation reaction. The implications of this result will be discussed in Chapter 3.

Experimental Procedures

General Considerations. All manipulations involving air-sensitive materials were conducted in a Vacuum Atmospheres glovebox under an atmosphere of argon or using standard Schlenk techniques under argon. THF was distilled under argon from sodium/benzophenone ketyl before use. Toluene was distilled under argon from molten sodium, and CH_2Cl_2 was distilled under nitrogen from CaH_2. Bis(trimethylphosphine)titanocene, $Cp_2Ti(PMe_3)_2$ was prepared from titanocene dichloride (obtained from Boulder Scientific, Boulder, CO) by the procedure of Binger et. al.,[36] and was stored in a glovebox under argon. Titanocene dicarbonyl is commercially available from Strem Chemicals, and is also readily synthesized from titanocene dichloride.[37] All other reagents were available from commercial sources and were used without further purification, unless otherwise noted.

Flash chromatography was performed on E. M. Science Kieselgel 60 (230-400 mesh) unless otherwise noted. Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^1H NMR analysis, and in the cases of unknown compounds, elemental analysis. Yields indicated in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly. All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopies. Previously unreported compounds were also characterized by elemental analysis (E & R Analytical Laboratory, Inc.). Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian XL-500, or a Varian Unity 300. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; qd, quartet of doublets; m, multiplet. All ^1H NMR spectra are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm

relative to deuterochloroform. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer. Gas chromatography (GC) analysis were performed on a Hewlet-Packard 5890 gas chromatograph with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase.

Preparation of Enone Substrates: All enone substrates were synthesized as described above and have been previously reported except for: **7-phenyl-6-heptyn-2-one:** Phenylacetylene (4.4 mL, 40 mmol) and diethyl ether (50 mL) were combined in a flame dried Schlenk flask under argon and cooled to 0 °C. A 1.6 M solution of*n*BuLi (25 mL, 40 mmol) was then added, and the solution was allowed to warm to room temperature. The diethyl ether was removed *in vacuo* and the lithium salt was dissolved in THF (10 mL) and anhydrous DMSO (20 mL) and cooled to 0 °C. 5-Chloro-2-pentanone ethylene ketal was added, and the solution was allowed to slowly warm to room temperature overnight. The reaction mixture was diluted with water (50 mL) and extracted with 3 x 50 mL diethyl ether. The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the resulting oil was purified by Kugelrohr distillation. The material was immediately dissolved in THF (20 mL) and 1 N HCl solution (20 mL) and stirred vigorously overnight. The reaction mixture was diluted with diethyl ether (100 mL), washed with brine (50 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil was purified by flash chromatography (hexane:ethyl acetate = 9:1) to afford 4.0 g (54 %) of a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (m, 2 H); 7.26 (m, 3 H); 2.61 (t, J = 6.9 Hz, 2 H); 2.43 (t, J = 7.1 Hz, 2 H); 2.31 (s, 3 H); 1.83 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0, 131.6, 128.3, 127.7, 123.9, 89.2, 81.4, 42.3, 30.1, 22.8, 18.8. IR (neat):

2938, 1715, 1598, 1490, 1441, 1369, 1158, 758, 692 cm^{-1}. Anal. calcd for $C_{13}H_{14}O$: C, 86.83; H, 7.58. Found: C, 86.60; H, 7.60.

General Procedure A: for the Conversion of Enones and Enals to γ-butyrolactones using $Cp_2Ti(PMe_3)_2$. In an argon filled glovebox, a dry sealable Schlenk flask is charged with the enone (0.5 mmol), $Cp_2Ti(PMe_3)_2$ (0.55 mmol), and toluene (2 mL). [Note: the enone was run through a plug of activated alumina in the glovebox and stored under argon.] The flask is removed from the glovebox, evacuated, backfilled with 12-15 psig CO and heated to 70 °C for 15-18 h. **Caution:** Appropriate precautions should be taken when performing reactions under elevated CO pressure. After cooling the reaction mixture to room temperature, the CO was cautiously released in the hood. The crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography.

General Procedure B: for the Conversion of Enones to γ-butyrolactones using *in situ* Generated $Cp_2Ti(PMe_3)_2$. On a Schlenk line under argon, a dry Schlenk flask charged with ground up Cp_2TiCl_2 (0.75 mmol) and toluene (2 mL) is cooled to -78 °C. *n*-BuLi (1.5 mmol) then PMe_3 (2.5 mmol) is added, and reaction is stirred at -78 °C for 1 h. The red solution is allowed to warm to room temperature, and the resulting brown solution is cannula-filtered into a dry sealable Schlenk flask containing the enone (0.5 mmol). The flask is then sealed, evacuated, backfilled with 12-15 psig CO, and heated to 70 °C for 15-18 h. **Caution:** Appropriate precautions should be taken when performing reactions under elevated CO pressure. After cooling the reaction mixture to room temperature, the CO was cautiously released in the

hood. The crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography.

***cis*-Hexahydro-6a-methyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 1):**[38] Procedure A was used to convert 6-hepten-2-one (67 mg, 0.6 mmol) to the desired product. Purification by flash chromatography (pentane: ethyl ether = 3: 1) afforded 60 mg (71 % yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.90 (dd, J = 9.8 Hz, J = 18.3 Hz, 1 H); 2.47 (m, 1 H); 2.33 (dd, J = 2.6 Hz, J = 18.4 Hz, 1 H); 2.11 (m, 1 H); 1.98 (m, 1 H); 1.5-1.8 (m, 4 H); 1.49 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 95.3, 43.7, 39.7, 36.6, 34.2, 25.3, 24.2. IR (neat): CO stretch: 1787; also 2964, 2872, 1272, 1225, 1193, 1150, 950, 732 cm^{-1}.

***cis*-Hexahydro-6a-methyl-6-*exo*-(ethyl-carboxylate)-2H-cyclopenta[b]furan-2-one (Table 2, entry 2):** Procedure A was used to convert ethyl-6-hepten-2-one-3-carboxylate (50 mg, 0.3 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl acetate = 4: 1) afforded 52 mg (91 % yield) of a colorless oil. Procedure B was also used to convert ethyl-6-hepten-2-one-3-carboxylate (98 mg, 0.53 mmol) to 95 mg (84 % yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (qd, J = 7.2 Hz, J = 2.2 Hz, 2 H); 3.08 (t, J = 6.8 Hz, 1 H); 2.87 (dd, J = 9.1 Hz, J = 18.2 Hz, 1 H); 2.58 (m, 1 H); 2.39 (dd, J = 1.9 Hz, J = 18.1 Hz, 1 H); 2.35 (m, 1 H); 1.98 (m, 2 H); 1.47 (m, 1 H); 1.44 (s, 3 H); 1.29 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 172.5, 95.5, 60.7, 54.7, 44.6, 36.0, 32.2, 28.3, 22.1, 14.2. IR (neat): CO stretches: 1774, 1729; also 2975, 1373, 1347, 1184, 1136, 1030, 954 cm^{-1}. Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.30; H, 7.64.

***cis*-Hexahydro-6a-methyl-5-*endo*-phenyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 3):** Procedure A was used to convert 4-phenyl-6-hepten-2-one (56 mg, 0.3 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl acetate = 5.7: 1) afforded 62 mg (93 % yield) of a colorless oil. Procedure B was also used to convert 4-phenyl-6-hepten-2-one (0.1 g, 0.53 mmol) to 90 mg (79 % yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (m, 5 H); 3.11 (m, 1 H); 2.86 (dd, J = 8.8 Hz, J = 18.2 Hz, 1 H); 2.41 (m, 4 H); 2.22 (t, J = 12.4 Hz, 1 H); 1.62 (m, 1 H); 1.54 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 142.2, 128.5, 126.8, 126.6, 93.9, 47.1, 45.0, 44.2, 41.7, 35.1, 26.6. IR (neat): CO stretch: 1765; also 2964, 2864, 1220, 1126, 954, 754, 700 cm^{-1}. Anal. calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.54; H, 7.57.

***cis*-Hexahydro-5,5-dimethyl-6a-methyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 4):** Procedure A was used to convert 4,4-dimethyl-6-hepten-2-one (70 mg, 0.5 mmol) to the desired product. Purification by flash chromatography (hexane: ether = 7: 3) afforded 76 mg (91% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78 (dd, J = 9 Hz, J = 18 Hz, 1 H); 2.58 (q, J = 9 Hz, 1 H); 2.32 (d, J = 18 Hz, 1 H); 2.01 (d, J = 14.4 Hz, 1 H); 1.86 (dd, J = 7.8 Hz, J = 14.4 Hz, 1 H); 1.71 (d, J = 14.4 Hz, 1 H); 1.44 (s, 3 H); 1.37 (m, 1 H); 1.06 (s, 3 H); 0.98 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 87.0, 44.4, 39.0, 35.5, 30.4, 26.5, 20.4, 19.9, 18.2. IR (neat): CO stretch: 1770; also 2956, 1463, 1381, 1249, 1178, 1123, 1056, 952, 926. Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.20; H, 9.71.

***cis*-Hexahydro-6a-*n*-propyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 5):** Procedure A was used to convert 8-nonen-4-one (70 mg, 0.5 mmol) to the desired product. Purification by flash chromatography (hexane: ether = 7: 3) afforded 80 mg (95% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83 (dd, *J* = 10 Hz, *J* = 18.5 Hz, 1 H); 2.49 (m, 1 H); 2.27 (dd, *J* = 2.5 Hz, *J* = 18.5 Hz, 1 H); 2.03 (m, 1 H); 1.86 (m, 1 H); 1.55 (m, 8 H); 0.92 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 89.3, 33.2, 32.6, 29.1, 28.1, 25.5, 15.0, 8.7, 5.4. IR (neat): CO stretch: 1767; also 2959, 1467, 1271, 1216, 1192, 1150, 973, 920. Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.20; H, 9.30.

***cis*-Hexahydro-5-aza-6a-methyl-5-*N*-phenyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 6):** A modification of procedure A utilzing 10 mL toluene was used to convert *N*-allyl-*N*-acetonyl aniline (94 mg, 0.5 mmol) to the desired product. Purification by flash chromatography (hexane: ether = 3: 7) afforded 80 mg (80% yield) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.1 Hz, 2 H); 6.72 (t, *J* = 7.5 Hz, 1 H); 6.55 (d, *J* = 8.1 Hz, 2 H); 3.76 (d, *J* = 11 Hz, 1 H); 3.46 (dd, *J* = 7.8 Hz, *J* = 10 Hz, 1 H); 3.26 (dd, *J* = 4.5 Hz, *J* = 10 Hz, 1 H); 3.15 (d, *J* = 11 Hz, 1 H); 2.90 (t, *J* = 9 Hz, 1 H); 2.78 (m, 1 H); 2.50 (dd, *J* = 2.7 Hz, *J* = 17.5 Hz, 1 H); 1.54 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 138.6, 120.4, 109.2, 104.5, 82.9, 50.8, 45.9, 34.4, 26.8, 15.1. IR (KBr): CO stretch: 1756: also 2958, 2837, 1604, 1506, 1246, 1188, 1101, 927, 756, 695. Mp = 116 - 118°C. Anal. calcd for $C_{12}H_{15}NO_2$: C, 71.87; H, 6.96. Found: C, 71.61; H, 6.75.

***cis*-Hexahydro-5,5(diethyl-dicarboxylate)-2H-cyclopenta[b]furan-2-one (Table 2, entry 7):** Procedure A was used to convert diethyl-5-hexen-1-al-3,3-dicarboxylate (0.121 g, 0.5 mmol) to the desired product. Purification by

flash chromatography (hexane: ethyl acetate = 7: 3) afforded 90 mg (66 % yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (m, 1 H); 4.20 (m, 4 H); 3.05 (m, 1 H); 2.77 (dd, *J* = 9.6 Hz, *J* = 18.1 Hz, 1 H); 2.68 (m, 2 H); 2.53 (dd, *J* = 2.0 Hz, *J* = 18.1 Hz, 1 H); 2.36 (d, *J* = 7.8 Hz, 2 H); 1.22 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5, 171.1, 170.7, 84.9, 62.1, 61.9, 60.5, 40.7, 39.8, 38.0, 35.8, 14.0 (2). IR (neat): CO stretches: 1778, 1727, 1737; also 2983, 1447, 1367, 1258, 1097, 1051, 862 cm^{-1}. Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.54. Found: C, 57.87; H, 6.71.

4,5,6,6a-tetrahydro-6a-methyl-3-phenyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 8): In an argon-filled glovebox, a dry Fischer-Porter bottle was charged with 7-phenyl-6-heptyn-2-one (186 mg, 1 mmol) $Cp_2Ti(PMe_3)_2$ (364 mg, 1.1 mmol), and toluene (5 mL). The bottle was removed from the glovebox, evacuated, backfilled with 20 psig CO, and heated to 85 °C for 24 h. After cooling to room temperature, the crude reaction mixture was directly loaded onto a column of activated alumina (ICN Biomedicals), and chromatography was performed (pentane: ethyl ether = 7: 3) to afford 60 mg (28 % yield) of a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (dt, *J* = 8.1 Hz, *J* = 1.6 Hz, 2 H); 7.41 (m, 3 H); 2.85 (m, 1 H); 2.72 (m, 1 H); 2.20 (m, 2 H); 2.05 (dd, *J* = 12.1 Hz, *J* = 7.0 Hz, 1 H); 1.59 (dd, *J* = 11.3 Hz, *J* = 21.9 Hz, 1 H); 1.54 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 163.9, 121.3, 119.7, 119.6, 119.3, 113.8, 80.2, 24.8, 15.6, 13.9, 13.8. IR (neat): CO stretch: 1746; also 2973, 1447, 1310, 1220, 1206, 1141, 970, 792, 696 cm^{-1}. Mp = 115 - 121 °C. Anal. calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.22; H, 6.39.

***cis*-Hexahydro-6a-phenyl-5-*endo*-phenyl-2H-cyclopenta[b]furan-2-one (Table 2, entry 9):** Procedure A was used to convert 1,4-diphenyl-6-

hepten-2-one (0.125 g, 0,5 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl acetate = 5.7: 1) yielded 74 mg (54 % yield) of a white solid. Additionally, in an argon filled glovebox, 1,4-diphenyl-6-hepten-2-one (0.125 g, 0.5 mmol), $Cp_2Ti(CO)_2$ (0.129 g, 0.55 mmol), and toluene (2 mL) were added to a dry sealable Schlenk flask. The flask was sealed, removed from the glovebox, and heated to 90 °C for 11 h. After cooling to room temperature, the crude reaction mixture was filtered through a plug of silica gel with diethyl ether and purified by flash chromatography (hexane: ethyl acetate = 9: 1) to afforded 112 mg (81 % yield) of a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 10 H); 3.53 (m, 1 H); 2.97 (m, 1 H); 2.4-2.8 (m, 5 H); 1.83 (q, *J* = 12.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 143.9, 142.2, 128.7, 128.7, 127.7, 126.9, 126.8, 123.9, 96.2, 49.6, 48.5, 46.0, 41.3, 34.1. IR (KBr pellet): CO stretch: 1775; also 3026, 2966, 1600, 1452, 1179, 970, 699 cm^{-1}. Mp = 89-91 °C. Anal. calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.80; H, 6.39.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-2H-indanyl[b]furan-2-one (Table 1, entry 10):** Procedure A was used to convert *o*-allylacetophenone (30 mg, 0.19 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl acetate = 4: 1) afforded 35 mg (98 % yield) of a clear oil. Procedure B was also used to convert *o*-allylacetophenone (86 mg, 0.54 mmol) to 0.10g (98 % yield) of the desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (m, 1 H); 7.28 (m, 3 H); 3.31 (dd, *J* = 7.1 Hz, *J* = 16.5 Hz, 1 H); 2.95 (m, 2 H); 2.83 (dd, *J* = 2.0 Hz, *J* = 16.5 Hz, 1 H); 2.40 (m, 1 H); 1.74 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 142.5, 141.1, 129.6, 127.6, 125.3, 124.2, 95.4, 44.2, 36.9, 36.6, 25.0. IR (neat): CO stretch: 1766; also 2929, 1442, 1379, 1206,

1066, 954, 768 cm^{-1}. Anal. calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.36; H, 6.54.

Metallacycle 6a: In an argon filled glovebox, diethyl-5-hexen-1-al-3,3-dicarboxylate (15 mg, 0.06 mmol), $Cp_2Ti(PMe_3)_2$ (20 mg, 0.06 mmol), and d^6-benzene (700 μL) were combined in an oven-dried resealable NMR tube. The vessel was removed from the glovebox, evacuated and backfilled with 12 psig CO and heated to 45 °C for 6 h. The reaction vessel was returned to the glovebox and the reaction mixture was filtered through a pad of celite. The solvent was removed *in vacuo*. The crystals were grown at -30 °C from a slowly evaporating THF solution. ^1H NMR (300 MHz, C_6D_6): δ 5.79 (s, 5 H); 5.52 (s, 5 H); 4.78 (q, J = 4.5 Hz, 1 H); 3.99 (m, 4 H); 2.62 (m, 2 H); 2.49 (m, 1 H); 2.20 (m, 4 H); 0.92 (m, 6 H).

X-ray Structure of 6a: The x-ray structure determination of metallacycle **6a** was conducted by Dr. William Davis using a Siemens SMART/CCD diffractometer at 188 K. A total of 3562 reflections were collected. The crystals are triclinic and in space group P1, with a = 8.5177(10) Å, b = 11.7520 Å, c = 12.1902(14) Å, α = 117.230(2)°, β = 95.322(2)°, and γ = 93.509(2)°. The refinement method used was a full-matrix least-squares fit on F^2, and the data converged with an agreement factor of R = 0.074. See following pages for more detailed information.

Crystal Structure Data for 9a

Table 3. Crystal data and structure refinement for **9a**.

Identification code	96004
Empirical formula	$C_{23}H_{28}O_6Ti$
Formula weight	448.35
Temperature	188(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.5177(10) Å α = 117.230(2)°
	b = 11.7520(14) Å β = 95.322(2)°
	c = 12.1902(14) Å γ = 93.509(2)°
Volume, Z	1072.9(2) Å^3, 2
Density (calculated)	1.388 Mg/m^3
Absorption coefficient	0.436 mm^{-1}
F(000)	472
Crystal morphology	prismatic
Crystal size	0.21 x 0.18 x 0.12 mm

B. Data Collection and Reduction

Diffractometer	Siemens SMART/CCD
Crystal-Detector distance	6.0 cm
Scan type	ω Scans
Scan angle	0.30°
θ range for data collection	1.90 to 21.00°
Limiting indices	$-7 \le h \le 9$, $-13 \le k \le 11$, $-13 \le l \le 13$
Reflections collected	3562
Independent reflections	2259 (R_{int} = 0.0583)
Absorption correction	None

C. Structure Solution and Refinement

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2216 / 0 / 272
Goodness-of-fit on F^2	1.183
Final R indices [I>2σ(I)]	R_1 = 0.0735, wR_2 = 0.1465
R indices (all data)	R_1 = 0.0878, wR_2 = 0.1939
Maximum shift/esd	0.003
Extinction coefficient	0.0060(14)
Largest diff. peak and hole	0.350 and -0.287 $e\dot{A}^{-3}$

Notes: E

$$R_1 = \sum|F_o|-|F_c|/\sum|F_o|$$

$$wR_2=[\sum[w(F_o^2-F_c^2)^2/[\sum(F_o^2)^2]]^{1/2}$$

Weighting scheme

calc w=1/[\s^2^(Fo^2^)+(0.0000P)^2^+4.8203P] where P=(Fo^2^+2Fc^2^)/3

Refinement on F^2 for ALL reflections. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The observed criterion of $F^2 > 2\sigma(F^2)$ is used only for calculating R_1 and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R- factors based on ALL data will be even larger.

Table 4. Atomic coordinates [x 10^4] and equivalent isopropic displacement parameters [$Å^2$ x 10^3] for **9a**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Ti	-1366(1)	7612(1)	15083(1)	28(1)
O(1)	-2881(5)	8158(4)	14305(4)	31(1)
O(2)	-2274(6)	4635(5)	13720(5)	58(2)
O(3)	-7332(8)	6756(7)	10612(7)	99(3)
O(4)	-2497(6)	9028(5)	12099(4)	45(1)
O(5)	-2866(6)	7025(5)	10560(5)	54(2)
O(6)	-5902(7)	8326(7)	10564(6)	89(2)
C(1)	-512(9)	8767(7)	17254(6)	42(2)
C(2)	-2039(10)	9093(8)	17072(6)	49(2)
C(3)	-3126(9)	7997(9)	16646(7)	49(2)
C(4)	-2279(9)	6989(8)	16566(7)	48(2)
C(5)	-667(8)	7447(7)	16941(6)	38(2)
C(6)	1123(8)	8540(7)	14896(7)	39(2)
C(7)	201(8)	8021(8)	13725(7)	41(2)
C(8)	-83(8)	6705(8)	13263(7)	45(2)
C(9)	697(8)	6384(7)	14134(8)	45(2)
C(10)	1463(8)	7510(8)	15114(7)	43(2)
C(11)	-2759(8)	5681(7)	14043(6)	37(2)
C(12)	-4567(8)	5644(7)	13721(7)	37(2)
C(13)	-5142(7)	6566(6)	13254(6)	33(2)
C(14)	-4559(7)	8003(6)	14068(6)	33(2)
C(15)	-5087(8)	8585(6)	13222(6)	35(2)
C(16)	-4781(7)	7583(6)	11906(6)	31(2)
C(17)	-4722(8)	6308(6)	11980(6)	35(2)
C(18)	-3259(8)	7999(7)	11559(7)	35(2)
C(19)	-6151(9)	7470(8)	10949(7)	42(2)
C(51)	-1426(9)	7263(8)	10107(8)	60(2)
C(52)	-1146(9)	6036(7)	9068(7)	55(2)
C(61)	-7101(11)	8354(15)	9629(11)	129(6)
C(62)	-6353(13)	8486(13)	8742(10)	110(4)

Table 5. Bond lengths [Å] and angles [°] for **9a**.

Ti-O(1)	1.846(4)	Ti-C(11)	2.219(7)
Ti-C(1)	2.368(7)	Ti-C(9)	2.381(7)
Ti-C(5)	2.384(7)	Ti-C(8)	2.384(7)
Ti-C(2)	2.398(7)	Ti-C(6)	2.403(7)
Ti-C(4)	2.410(7)	Ti-C(7)	2.411(7)
Ti-C(10)	2.417(7)	Ti-C(3)	2.430(7)
O(1)-C(14)	1.415(7)	O(2)-C(11)	1.219(8)
O(3)-C(19)	1.179(9)	O(4)-C(18)	1.189(8)
O(5)-C(18)	1.324(8)	O(5)-C(51)	1.454(8)
O(6)-C(19)	1.305(9)	O(6)-C(61)	1.472(10)
C(1)-C(2)	1.405(10)	C(1)-C(5)	1.411(10)
C(2)-C(3)	1.392(11)	C(3)-C(4)	1.395(11)
C(4)-C(5)	1.397(10)	C(6)-C(10)	1.394(10)
C(6)-C(7)	1.401(10)	C(7)-C(8)	1.378(10)
C(8)-C(9)	1.407(10)	C(9)-C(10)	1.381(10)
C(11)-C(12)	1.546(9)	C(12)-C(13)	1.522(9)
C(13)-C(17)	1.522(9)	C(13)-C(14)	1.535(9)
C(14)-C(15)	1.526(9)	C(15)-C(16)	1.554(9)
C(16)-C(18)	1.520(9)	C(16)-C(19)	1.526(10)
C(16)-C(17)	1.546(9)	C(51)-C(52)	1.472(10)
C(61)-C(62)	1.367(13)		

O(1)-Ti-C(11)	86.1(2)	O(1)-Ti-C(1)	121.8(2)
C(11)-Ti-C(1)	127.3(3)	O(1)-Ti-C(9)	125.4(2)
C(11)-Ti-C(9)	80.9(3)	C(1)-Ti-C(9)	107.7(3)
O(1)-Ti-C(5)	142.8(2)	C(11)-Ti-C(5)	95.6(3)
C(1)-Ti-C(5)	34.6(2)	C(9)-Ti-C(5)	91.4(3)
O(1)-Ti-C(8)	91.2(2)	C(11)-Ti-C(8)	79.4(3)
C(1)-Ti-C(8)	135.4(3)	C(9)-Ti-C(8)	34.3(2)
C(5)-Ti-C(8)	125.7(3)	O(1)-Ti-C(2)	90.0(2)
C(11)-Ti-C(2)	118.9(3)	C(1)-Ti-C(2)	34.3(2)
C(9)-Ti-C(2)	141.9(3)	C(5)-Ti-C(2)	56.7(3)
C(8)-Ti-C(2)	161.7(3)	O(1)-Ti-C(6)	104.6(2)
C(11)-Ti-C(6)	134.1(3)	C(1)-Ti-C(6)	84.9(3)
C(9)-Ti-C(6)	56.2(2)	C(5)-Ti-C(6)	100.7(3)
C(8)-Ti-C(6)	56.2(3)	C(2)-Ti-C(6)	105.9(3)
O(1)-Ti-C(4)	115.4(2)	C(11)-Ti-C(4)	71.6(3)
C(1)-Ti-C(4)	56.5(3)	C(9)-Ti-C(4)	110.0(3)
C(5)-Ti-C(4)	33.9(2)	C(8)-Ti-C(4)	138.3(3)
C(2)-Ti-C(4)	55.8(3)	C(6)-Ti-C(4)	134.6(3)
O(1)-Ti-C(7)	80.2(2)	C(11)-Ti-C(7)	109.9(3)
C(1)-Ti-C(7)	117.7(3)	C(9)-Ti-C(7)	56.0(3)
C(5)-Ti-C(7)	132.5(2)	C(8)-Ti-C(7)	33.4(2)
C(2)-Ti-C(7)	129.4(3)	C(6)-Ti-C(7)	33.8(2)
C(4)-Ti-C(7)	164.3(3)	O(1)-Ti-C(10)	135.3(2)
C(11)-Ti-C(10)	112.5(3)	C(1)-Ti-C(10)	79.7(3)
C(9)-Ti-C(10)	33.4(2)	C(5)-Ti-C(10)	78.0(2)
C(8)-Ti-C(10)	55.9(3)	C(2)-Ti-C(10)	112.3(3)
C(6)-Ti-C(10)	33.6(2)	C(4)-Ti-C(10)	109.1(3)
C(7)-Ti-C(10)	55.5(2)	O(1)-Ti-C(3)	86.9(2)
C(11)-Ti-C(3)	85.4(3)	C(1)-Ti-C(3)	56.5(3)
C(9)-Ti-C(3)	143.4(3)	C(5)-Ti-C(3)	56.4(2)
C(8)-Ti-C(3)	164.8(3)	C(2)-Ti-C(3)	33.5(3)
C(6)-Ti-C(3)	138.7(3)	C(4)-Ti-C(3)	33.5(3)
C(7)-Ti-C(3)	159.1(3)	C(10)-Ti-C(3)	132.9(2)

C(14)-O(1)-Ti	136.3(4)	C(18)-O(5)-C(51)	116.7(6)
C(19)-O(6)-C(61)	118.8(7)	C(2)-C(1)-C(5)	107.5(7)
C(2)-C(1)-Ti	74.1(4)	C(5)-C(1)-Ti	73.3(4)
C(3)-C(2)-C(1)	108.6(7)	C(3)-C(2)-Ti	74.5(4)
C(1)-C(2)-Ti	71.7(4)	C(2)-C(3)-C(4)	107.6(7)
C(2)-C(3)-Ti	72.0(4)	C(4)-C(3)-Ti	72.5(4)
C(5)-C(4)-C(3)	109.1(7)	C(5)-C(4)-Ti	72.0(4)
C(3)-C(4)-Ti	74.0(4)	C(4)-C(5)-C(1)	107.2(7)
C(4)-C(5)-Ti	74.1(4)	C(1)-C(5)-Ti	72.1(4)
C(10)-C(6)-C(7)	107.1(6)	C(10)-C(6)-Ti	73.8(4)
C(7)-C(6)-Ti	73.4(4)	C(8)-C(7)-C(6)	108.6(7)
C(8)-C(7)-Ti	72.2(4)	C(6)-C(7)-Ti	72.8(4)
C(7)-C(8)-C(9)	107.8(7)	C(7)-C(8)-Ti	74.4(4)
C(9)-C(8)-Ti	72.7(4)	C(10)-C(9)-C(8)	107.7(7)
C(10)-C(9)-Ti	74.7(4)	C(8)-C(9)-Ti	72.9(4)
C(9)-C(10)-C(6)	108.7(7)	C(9)-C(10)-Ti	71.8(4)
C(6)-C(10)-Ti	72.6(4)	O(2)-C(11)-C(12)	115.5(6)
O(2)-C(11)-Ti	127.6(5)	C(12)-C(11)-Ti	116.8(5)
C(13)-C(12)-C(11)	118.3(5)	C(17)-C(13)-C(12)	115.2(6)
C(17)-C(13)-C(14)	103.0(5)	C(12)-C(13)-C(14)	117.0(5)
O(1)-C(14)-C(15)	109.7(5)	O(1)-C(14)-C(13)	108.8(5)
C(15)-C(14)-C(13)	102.6(5)	C(14)-C(15)-C(16)	104.5(5)
C(18)-C(16)-C(19)	107.8(6)	C(18)-C(16)-C(17)	112.7(5)
C(19)-C(16)-C(17)	111.1(6)	C(18)-C(16)-C(15)	111.4(6)
C(19)-C(16)-C(15)	109.0(5)	C(17)-C(16)-C(15)	104.8(5)
C(13)-C(17)-C(16)	106.8(5)	O(4)-C(18)-O(5)	123.9(6)
O(4)-C(18)-C(16)	126.3(7)	O(5)-C(18)-C(16)	109.8(6)
O(3)-C(19)-O(6)	122.2(7)	O(3)-C(19)-C(16)	126.6(7)
O(6)-C(19)-C(16)	111.2(6)	O(5)-C(51)-C(52)	107.6(6)
C(62)-C(61)-O(6)	109.1(8)		

Symmetry transformations used to generate equivalent atoms:

Table 6. Anisotropic displacement parameters [$Å^2 \times 10^3$] for **9a**. The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Ti	21(1)	30(1)	35(1)	18(1)	5(1)	3(1)
O(1)	23(3)	35(3)	34(3)	16(2)	6(2)	1(2)
O(2)	53(3)	32(3)	86(4)	29(3)	-8(3)	4(3)
O(3)	51(4)	122(6)	136(7)	88(5)	-50(4)	-37(4)
O(4)	44(3)	42(3)	43(3)	18(3)	1(3)	-10(3)
O(5)	47(3)	43(3)	53(4)	6(3)	26(3)	-7(3)
O(6)	48(4)	152(6)	117(6)	118(6)	-35(4)	-28(4)
C(1)	42(5)	44(5)	31(4)	14(4)	-5(4)	-2(4)
C(2)	68(6)	47(5)	27(4)	10(4)	13(4)	25(5)
C(3)	24(4)	94(7)	34(5)	35(5)	5(4)	7(5)
C(4)	38(5)	69(6)	53(5)	44(5)	6(4)	-8(4)
C(5)	38(5)	45(5)	42(4)	29(4)	5(4)	9(4)
C(6)	26(4)	34(4)	54(5)	17(4)	16(4)	1(3)
C(7)	27(4)	61(6)	49(5)	36(4)	11(4)	5(4)
C(8)	23(4)	59(6)	43(5)	15(4)	11(4)	7(4)
C(9)	31(4)	35(5)	70(6)	22(5)	20(4)	14(4)
C(10)	20(4)	71(6)	43(5)	31(5)	8(3)	6(4)
C(11)	36(4)	37(5)	41(4)	23(4)	0(3)	-4(4)
C(12)	31(4)	37(4)	42(4)	20(4)	3(3)	-4(3)
C(13)	16(4)	40(4)	40(4)	17(4)	4(3)	-4(3)
C(14)	20(4)	44(5)	33(4)	15(4)	6(3)	4(3)
C(15)	28(4)	34(4)	38(4)	12(4)	5(3)	10(3)
C(16)	23(4)	40(4)	35(4)	21(4)	5(3)	6(3)
C(17)	24(4)	41(4)	38(4)	15(4)	9(3)	5(3)
C(18)	29(4)	37(5)	38(5)	18(4)	-2(4)	-2(4)
C(19)	32(5)	55(5)	43(5)	27(4)	2(4)	6(4)
C(51)	47(5)	59(6)	72(6)	25(5)	32(5)	-6(4)
C(52)	51(5)	56(5)	61(6)	29(5)	20(4)	-1(4)
C(61)	43(6)	288(18)	136(10)	176(13)	-22(6)	-20(8)
C(62)	84(8)	166(12)	90(8)	79(9)	-30(7)	-20(8)

Table 7. Hydrogen coordinates (x 10^4) and isotropic displacement parameters [$Å^2$ x 10^3] for **9a**.

	x	y	z	U(eq)
H(1A)	450(9)	9331(7)	17536(6)	50
H(2A)	-2288(10)	9923(8)	17215(6)	58
H(3A)	-4241(9)	7945(9)	16446(7)	59
H(4A)	-2726(9)	6129(8)	16300(7)	57
H(5A)	168(8)	6961(7)	16978(6)	46
H(6A)	1455(8)	9427(7)	15439(7)	46
H(7A)	-167(8)	8497(8)	13319(7)	49
H(8A)	-697(8)	6119(8)	12492(7)	54
H(9A)	698(8)	5544(7)	14061(8)	54
H(10A)	2113(8)	7572(8)	15820(7)	51
H(12A)	-4979(8)	4756(7)	13080(7)	44
H(12B)	-5062(8)	5809(7)	14476(7)	44
H(13A)	-6327(7)	6474(6)	13185(6)	39
H(14A)	-5048(7)	8377(6)	14856(6)	40
H(15A)	-4459(8)	9426(6)	13487(6)	42
H(15B)	-6226(8)	8707(6)	13233(6)	42
H(17A)	-5493(8)	5620(6)	11313(6)	42
H(17B)	-3647(8)	6031(6)	11882(6)	42
H(51A)	-516(9)	7584(8)	10781(8)	72
H(51B)	-1552(9)	7919(8)	9819(8)	72
H(52A)	-179(9)	6167(7)	8742(7)	82
H(52B)	-2051(9)	5729(7)	8406(7)	82
H(52C)	-1021(9)	5395(7)	9364(7)	82
H(61A)	-7839(11)	7546(15)	9239(11)	155
H(61B)	-7725(11)	9085(15)	10034(11)	155
H(62A)	-7146(13)	8505(13)	8116(10)	166
H(62B)	-5745(13)	7756(13)	8341(10)	166
H(62C)	-5632(13)	9290(13)	9134(10)	166

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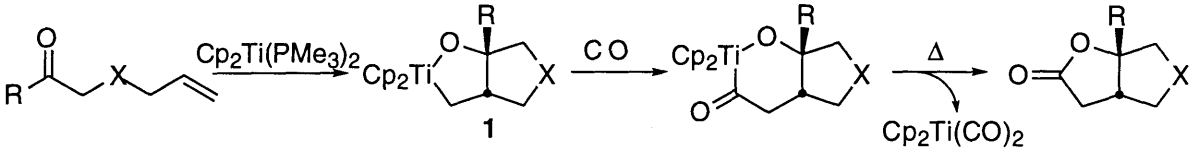
CHAPTER 3

TITANOCENE-CATALYZED CYCLOCARBONYLATION OF *o*-ALLYL ARYL KETONES TO γ-BUTYROLACTONES

Introduction

The "hetero Pauson-Khand" reaction described in Chapter 2 is the first completely diastereoselective synthesis of γ-butyrolactones from the condensation of an alkene, a carbonyl moiety, and CO (Scheme 1).[1] In a single process, two carbon-carbon bonds and two rings are constructed. A drawback to the method is the need to use a stoichiometric amount of the metal complex to carry out the reaction. A catalytic variant of this procedure would be a significant improvement. This would not only decrease the amount of waste produced by the reaction, but would also make the potential use of expensive chiral catalysts more feasible.

Scheme 1

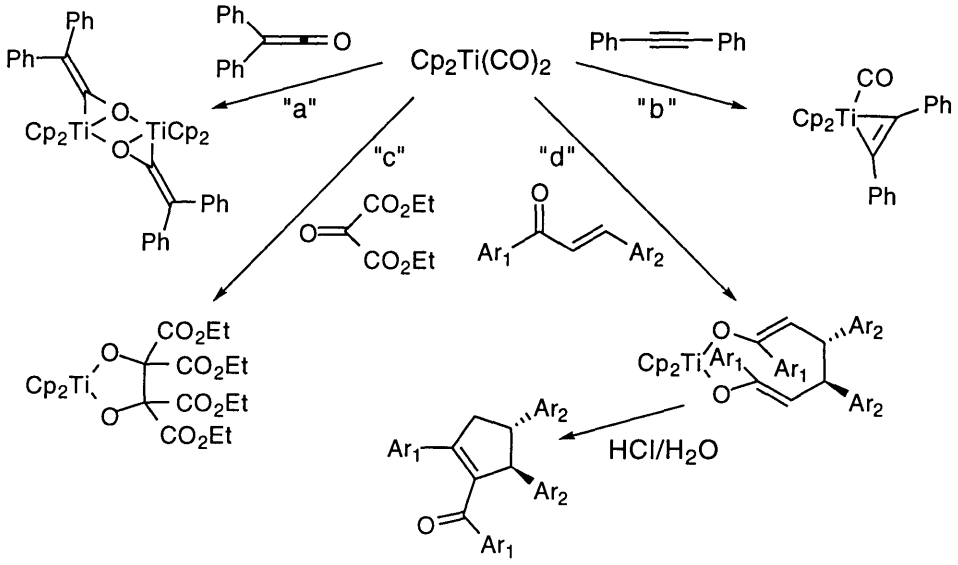


In order to develop a catalytic reaction sequence, the metal coproduct of the initial cyclization, $Cp_2Ti(CO)_2$, must be induced to react again with the enone substrate. The metal coproduct is in the same oxidation state as the original titanocene reagent, $Cp_2Ti(PMe_3)_2$, and the titanocene fragment remains intact, therefore making a catalytic cycle feasible. Trimethylphosphine is a relatively labile ligand and participates primarily in σ-bonding interactions with the titanium. However, CO forms much stronger bonds with the titanium center than does PMe_3 because there are empty π^* orbitals available on the CO that allow it to participate in backbonding interactions with the titanium.[2] Therefore, $Cp_2Ti(CO)_2$ is relatively unreactive and does not form oxametallacycles, **1**, with most enones under thermal conditions.

Titanocene dicarbonyl, however, is not an inert complex, and as alluded to in Chapter 2, it does react in some cases. $Cp_2Ti(CO)_2$ has previously been shown to react with ketenes,[3] acetylenes,[4,5] and CO_2 equivalents[6] (Scheme 2,

a, b, and c respectively). More recently it was reported that $Cp_2Ti(CO)_2$ also reacts with α,β-unsaturated aryl ketones[7] (Scheme 2d). This encouraged us to try to find a class of enone substrates that would also react with titanocene dicarbonyl, opening the way to the development of a catalytic process.

Scheme 2

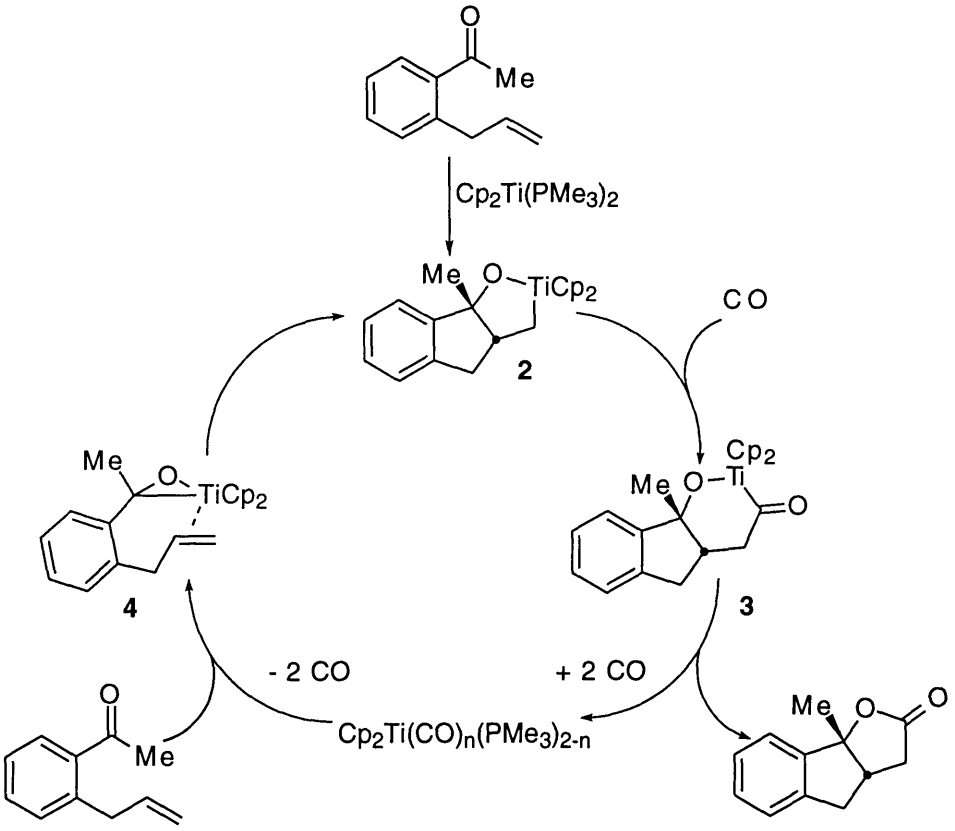


Results and Discussion:

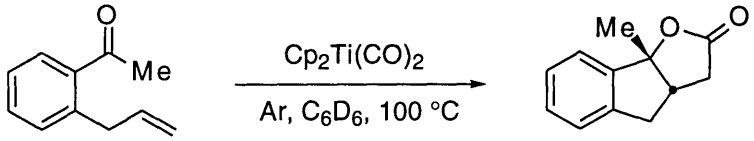
We have found that conjugated aromatic ketones with a suitably positioned olefin can be converted to γ-butyrolactones using a catalytic amount of the metal complex. In general, the substrates feature a keto moiety and an allyl group situated in an *ortho*-relationship on an aromatic ring. For example, in our initial communication we reported that *o*-allyl acetophenone can be converted to the corresponding lactone in excellent yield using 10 mol % $Cp_2Ti(PMe_3)_2$.[1] The proposed catalytic cycle is shown in Scheme 3. As mentioned above, the key to rendering the cyclocarbonylation catalytic is the ability of *o*-allyl acetophenone to react with the $Cp_2Ti(CO)_2$ (or possibly the mixed ligand catalyst $Cp_2Ti(CO)(PMe_3)$, *vide infra*) coproduct to form oxametallacycle **2**. In support of the viability of this step in the catalytic cycle, we have found that in a stoichiometric reaction, *o*-allyl acetophenone reacts

directly with $Cp_2Ti(CO)_2$ to form the γ-butyrolactone upon heating under an atmosphere of argon (Scheme 4).

Scheme 3

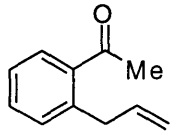
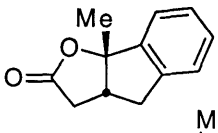
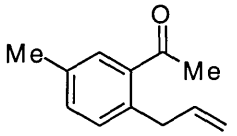
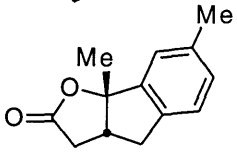
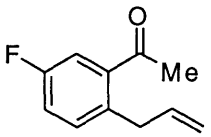
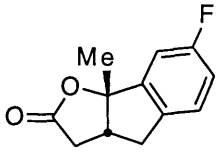
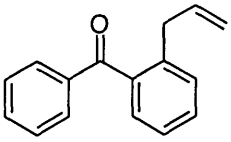
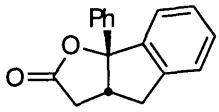
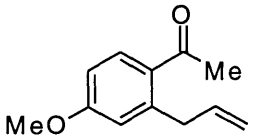
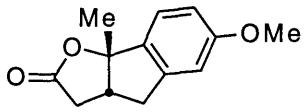
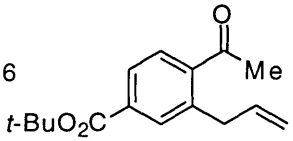
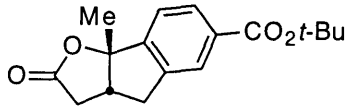
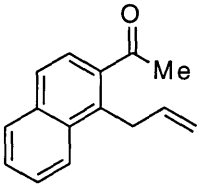
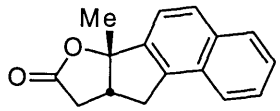
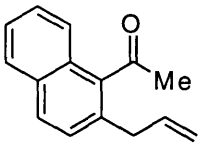
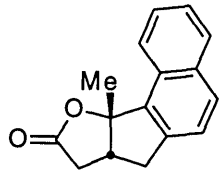
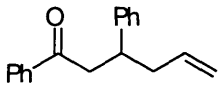
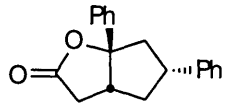
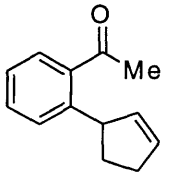
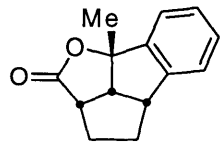


Scheme 4



Synthetic Results: Table 1 shows the results of the catalytic conversion of *o*-allyl aryl ketones to γ-butyrolactones under the conditions in Scheme 5. Catalyst levels range from 5 % to 20 % depending on the nature of the substrate (*vide infra*). This methodology tolerates various functional groups such as aryl

Table 1: Results of the Catalytic "Hetero Pauson-Khand" Reaction.

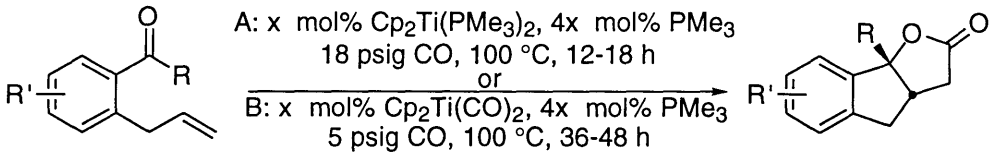
Entry	Substrate	Product	% cat. (cat. system)[a]	% PMe_3	Yield (%)[b]
1			7.5 (A) 7.5 (B)	30 30	91 96
2			10 (A) 7.5 (B)	— 30	89 84
3			10 (A)	40	80
4			5 (A) 5 (B)	20 20	97 94
5			20 (A)	50	74
6			7.5 (A)	30	93
7			10 (A)	40	87
8			7.5 (A) 7.5 (B)	30 30	92 94
9[c]			20 (B)	100	81
10			10 (A) 5 (B)	40 20	82 84

[a] System A: $Cp_2Ti(PMe_3)_2$, 18 psig CO, PMe_3, toluene, 12-18 h. System B: $Cp_2Ti(CO)_2$, 5 psig CO, PMe_3, toluene, 36-48 h. [b] Yields (an average of 2 or more runs) refer to isolated compound of >95% purity as assessed by ^1H NMR, GC, and elemental analysis. [c] Isolated as a 14:1 mixture of isomers.

fluorides (entry 3), ethers (entry 5), and esters (entry 6). We have shown that catalytic activity is not limited to *o*-allyl acetophenone derivatives, since allyl acetonapthones (entries 7 and 8) and allyl benzophenones (entry 4) are also viable substrates, as is the acyclic acetophenone featured in entry 9.

Scheme 5 shows the two catalyst systems that have been developed for this transformation. The original system (A) uses $Cp_2Ti(PMe_3)_2$ as the catalyst and is run at 18 psig CO for 12-18 h. The addition of excess PMe_3 was found to decrease the amount of catalyst necessary for complete conversion to the product.[8] The second catalyst system (B) uses the commercially available $Cp_2Ti(CO)_2$[9] as the catalyst and is run at only 5 psig CO. In this system, excess PMe_3 is also required.[10] We believe that the excess PMe_3 might be necessary to produce $Cp_2Ti(PMe_3)(CO)$,[11] which may act as a more efficient catalyst than titanocene dicarbonyl, due to the lability of the PMe_3 ligand and/or for electronic reasons. $Cp_2Ti(PMe_3)(CO)$ has been shown to form when $Cp_2Ti(PMe_3)_2$ is heated under CO pressure or when $Cp_2Ti(CO)_2$ is heated in the presence of PMe_3.[12] Trimethylphosphine may also play a role in facilitating the ligand-induced reductive elimination[13] of the organic fragment from intermediate **3**, since PMe_3 is a stronger σ-donor than CO and is in general a better ligand for d^0 Ti(IV) complexes.

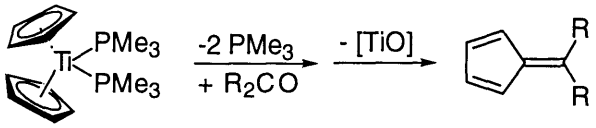
Scheme 5



While most of the substrates are cyclocarbonylated efficiently using either catalyst system, substrates that contain structural attributes that make them more difficult to cyclize are transformed more efficiently using $Cp_2Ti(CO)_2$ as a catalyst. We believe that such substrates can participate in destructive side reactions with $Cp_2Ti(PMe_3)_2$ due to the higher reactivity (lability of the PMe_3

ligands) of the complex compared to $Cp_2Ti(CO)_2$; the "titanocene" is thus destroyed before it can enter into the catalytic cycle.[14] For example, ketones have been shown to react with the cyclopentadienyl rings of $Cp_2Ti(PMe_3)_2$ under some conditions to form fulvenes with concommitant destruction of the titanocene framework (Scheme 6). While we see no evidence for the formation of fulvenes in the reaction mixture, similar destructive reactions may be taking place.

Scheme 6



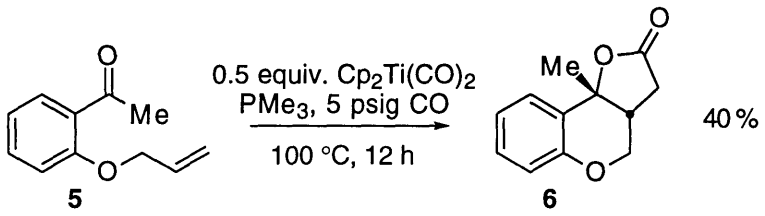
The substrate in entry 9 is difficult to cyclize because of the steric bulk of the phenyl-ketone substituent and the lack of a fused phenyl ring in the backbone holding the reactive fragments in close proximity, as discussed in Chapter 2. While $Cp_2Ti(PMe_3)_2$ is an ineffective catalyst for the cyclization of the substrate in entry 9, it is successfully cyclized using $Cp_2Ti(CO)_2$. This reasoning also extends to the stoichiometric results for this substrate as described in Chapter 2.

A second example of a more efficient catalytic cyclocarbonylation using titanocene dicarbonyl is demonstrated in entry 10, in which the substrate contains a 1,2-disubstituted olefin. Typically, titanocene-mediated and -catalyzed reductive cyclizations have been unable to utilize 1,2-disubstituted olefinic substrates. This is presumably due to the unfavorable steric interactions between the substituted olefin and the cyclopentadienyl rings[15,16] (zirconocene systems have been shown to accommodate such substrates due to the larger size of the metal coordination site).[17] Neither the procedure for catalytic reductive cyclization discussed in Chapter 1 nor the catalytic enyne cyclization which utilizes $Cp_2Ti(PMe_3)_2$ and isonitriles[15] were applicable to substrates

containing 1,2-disubstituted olefins. While the substrate in entry 10 is cyclized using 10 mol % of the $Cp_2Ti(PMe_3)_2$ catalyst, it can undergo the same transformation to the tetracyclic γ-butyrolactone using only 5 mol % $Cp_2Ti(CO)_2$. It should be noted that the related cyclocarbonylation of enynes using the titanocene dicarbonyl catalyst is also tolerant of olefin substitution.[18]

The stoichiometric use of $Cp_2Ti(CO)_2$ has allowed us to expand the scope of this hetero Pauson-Khand-type methodology to another problematic enone substrate. Acetophenone derivative **5** does not form any metallacycle upon reaction with $Cp_2Ti(PMe_3)_2$. The cyclization of other 1,7-enones with $Cp_2Ti(PMe_3)_2$ to form 6-membered rings has been attempted by us[16,19] and others[20,21] with no success. However, **5** reacts with 0.5 equivalents of $Cp_2Ti(CO)_2$ under the conditions shown to form the 6,6,5-tricyclic γ-butyrolactone, **6** (Scheme 7). While this substrate is not transformed to the lactone catalytically, it is the first example of the cyclization of an enone to form a 6-membered ring using a titanocene reagent.

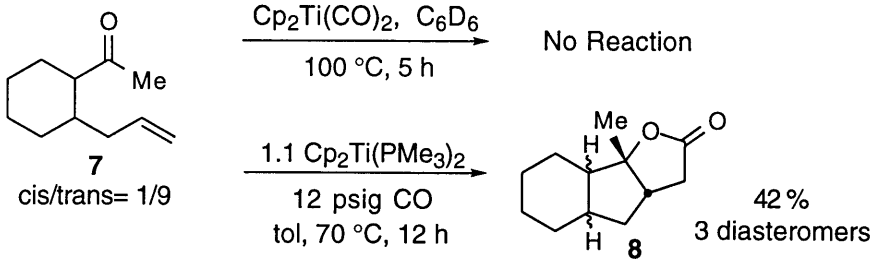
Scheme 7



Catalytic Activity: We originally considered two explanations for the increased reactivity of *o*-allyl aryl ketones: a steric argument and an electronic one. Sterically, the cyclization of *ortho*-allyl acetophenone by titanocene complexes might be enhanced since the ketone and the alkene are held in proximity by the rigid benzene ring in the backbone. Indeed, in our catalytic reductive cyclization methodology which converts enones to cyclopentanols, *o*-allyl acetophenone proved to be the optimal substrate.[16] However, the *cis/trans*

mixture (*cis/trans* = 1: 9) of the similarly constrained 1-acetyl-2-allyl cyclohexane, **7**,[22] fails to react with $Cp_2Ti(CO)_2$ (Scheme 8). Although this is not a conclusive experiment, if the reactivity of allyl acetophenones is derived solely from steric effects, one would expect at most 10 % (the *cis* isomer) of the enone to be converted to the lactone. Note that 1-acetyl-2-allyl cyclohexane can be cyclocarbonylated to a mixture of isomers of the corresponding γ-butyrolactone, **8**, using the stoichiometric conditions.

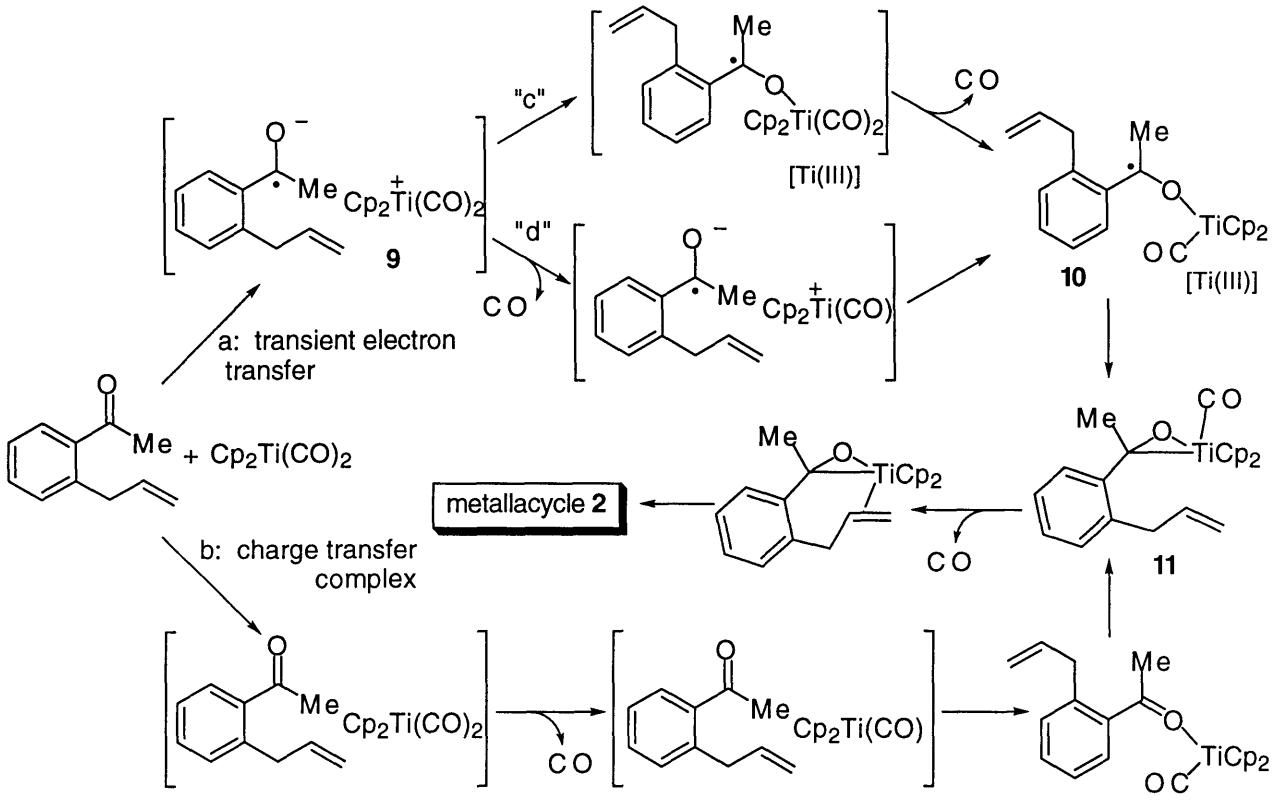
Scheme 8



We believe that olefinic aryl ketone derivatives can be converted to γ-butyrolactones catalytically because of their ability to displace the CO ligands on $Cp_2Ti(CO)_2$ to form a metallacycle either by transient electron transfer (Scheme 9, pathway "a") or by forming a charge transfer complex (Scheme 9, pathway "b").[23] Both of these possible pathways rely on acetophenone acting as an electron acceptor[24] for the titanium center; the shift in electron density away from the titanium reduces the backbonding interactions with the carbonyl ligands, labilizing them towards dissociative substitution by the enone substrate.[25] In pathway "a", a formal electron transfer is proposed, resulting in the ketyl radical of the acetophenone and a titanium cation as the tight ion pair, **9**. The formation of the Ti(III) alkoxide complex, **10**, can either proceed *via* a pentacoordinate Ti-alkoxide complex followed by loss of CO (pathway "c") or by dissociation of the CO followed by alkoxide formation (pathway "d"). Collapse of the diradical **10** leads to the Ti(IV)-ketone complex, **11**. The alkene replaces the remaining carbonyl ligand and then cyclization leads to metallacycle **2**. In

pathway "b", a charge transfer complex is formed in which no formal change in oxidation state occurs, but a shifting of electron density within the complex[26] away from the titanium center causes the labilization of the first carbonyl ligand and the subsequent formation of metallacycle **2**.

Scheme 9

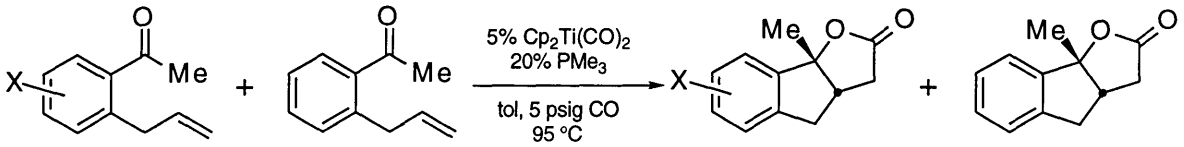


In the related intramolecular McMurry-type reactions[28] of oxo amides to indoles using low-valent titanium catalysts,[29,30] Fürstner has provided evidence for an aryl titanaoxacyclopropane species similar to **11** as an intermediate in the process.[29] In accord with our preliminary results, they have found that there is a correlation between the electronic properties of the aryl ketone and the rate of the reaction; diaryl ketones react significantly faster than aryl-alkyl ketones.

We have carried out relative rate experiments to quantify our results, and the data are shown in Table 2. Competition experiments were run between *o*-allyl acetophenone and the enone in question under the conditions shown in Scheme 10, and the reactions were allowed to progress to less than 10 %

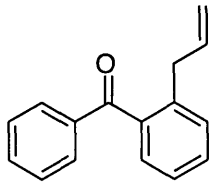
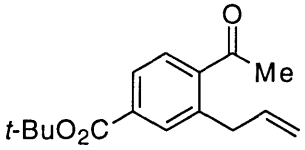
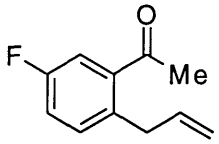
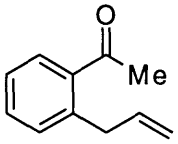
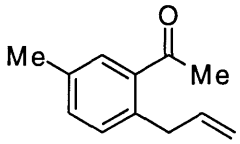
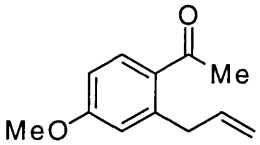
conversion. The relative concentration of the two products were determined versus an internal standard using gas chromatography. [Note: the rate of reaction of *o*-allyl benzophenone is greater than 20 times that of *o*-allyl acetophenone, so *o*-allyl benzophenone was run against 4'-*t*-butyl-carboxylate-6'-allylacetophenone to determine the relative rate.]

Scheme 10



There is a correlation between the electronic properties of the substrate and the rate of the reaction. The greatly enhanced rate of the benzophenone derivative compared to the acetophenone derivatives may reflect the larger reduction potential of benzophenone as compared to acetophenone.[27] Additionally, in the acetophenone series it is found that electron withdrawing groups on the aromatic ring of the substrate accelerate the reaction, presumably by augmenting the ability of the substrate to accept electron density from the titanocene species. A Hammett analysis was also carried out using this data, and the ρ value was determined to be 2.0 ± 0.2, which shows a strong dependence of the rate of the reaction on the electronic properties of the substrate.[31] The linear plot is shown in Figure 1.

Table 2: Relative rates of enone substrates of varying electronic properties.

entry	substrate	relative rate
1		26.5
2		5.64
3		3.91
4		1
5		0.66
6		0.36

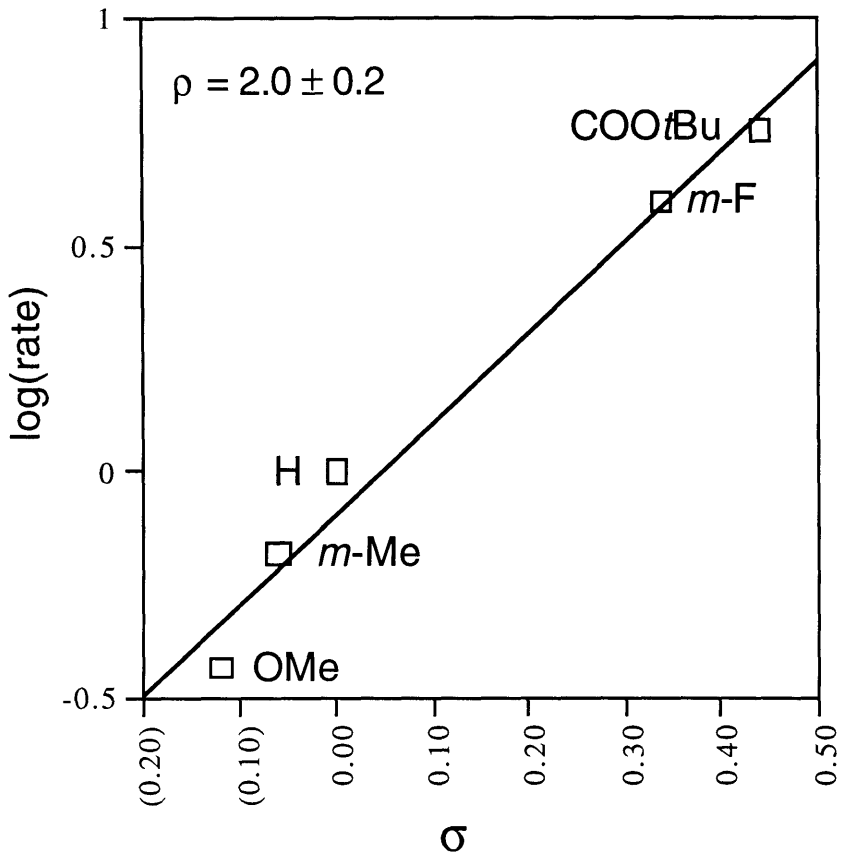


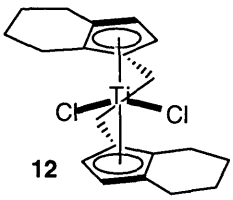
Figure 1: Hammett plot of the catalytic Hetero Pauson-Khand reaction. Reactions were run at 95 °C with 5 mol % $Cp_2Ti(CO)_2$, 20 mol % PMe_3, in toluene against biphenyl as an internal standard. (See experimental section for error analysis.)

Enantioselective Catalytic "Hetero Pauson-Khand" reaction:

One of the ultimate goals of this work is the development of a catalytic asymmetric version. In this scenario the chirality of a metal catalyst is used many times to produce multiple copies of a chiral organic product. The value of compounds with high levels of enantiopurity has made this field an active area of research both in industrial and academic settings.[32] Titanocene catalysts

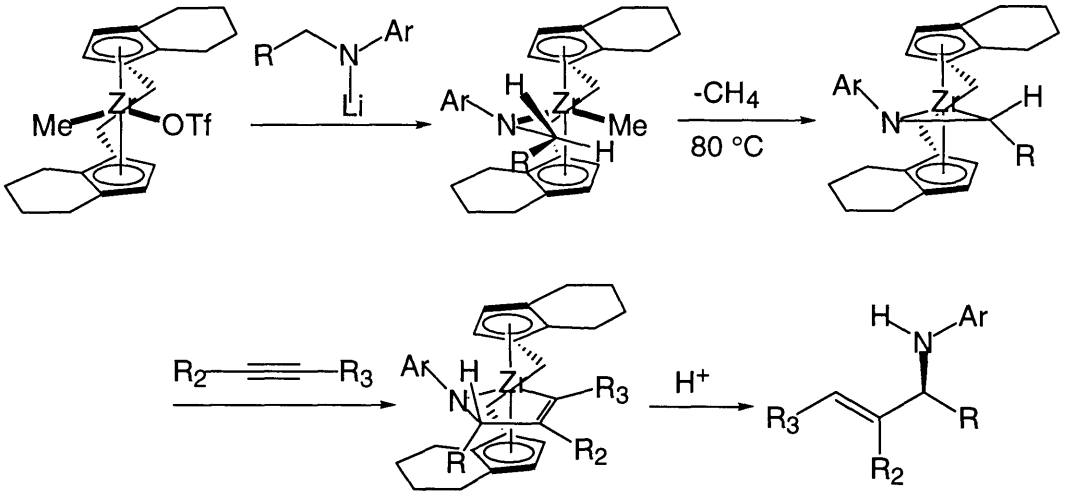
have particular potential in this area since there is a substantial body of research involving the replacement of cyclopentadienyl rings with a variety of chiral ligands.[33]

Optically active ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium [(EBTHI)Ti] derivatives, first developed by Brintzinger, have been used by a number of groups to carry out enantioselective organic transformations.[34] The Buchwald group has extensively explored the use of (EBTHI)$TiCl_2$ (**12**) as the precatalyst for the enantioselective hydrogenations of unsaturated organic compounds such as of imines,[35] enamines,[36] and tri-substituted olefins,[37] as well as for the hydrosilation of aryl ketones[38] and imines.[39] The use of these ligands has also been extended to the enantioselective formation of carbon-carbon bonds. The first efforts in this area were made by Dr. Robert Grossman in the enantioselective synthesis of allylic amines using ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium complexes as shown in Scheme 11.[40]



12

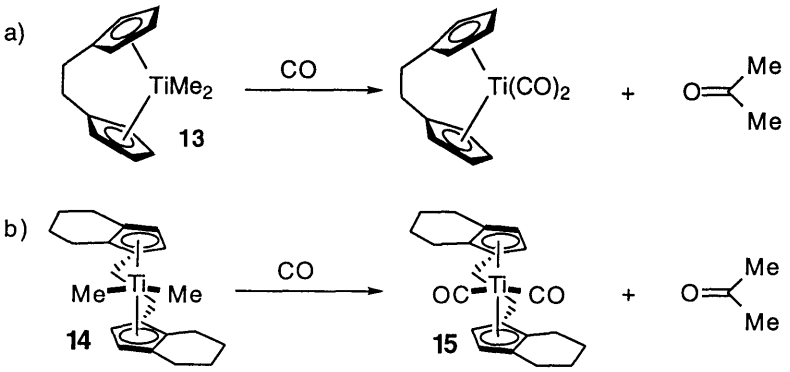
Scheme 11



Until recently, the extension of our titanocene-catalyzed reductive cyclization reactions to enantioselective variants based on the Brintzinger ligand has been hindered by the difficulty in accessing the Ti(II) oxidation state

for bridged titanocene systems. Brintzinger has studied the reactivity of the related ethylene-bridged titanocene dichloride derivative, $(CH_2)_2(C_5H_4)_2TiCl_2$, and has found that while it resembles the reactivity of its unbridged counterpart titanocene dichloride in transformations involving the Ti(III) and Ti(IV) oxidation states, it does not follow most reaction pathways that involve an intermediate in the Ti(II) oxidation state.[41] Brintzinger postulates that these reactions are blocked by the instability of the "free" bridged titanocene(II) species, $[(CH_2)_2(C_5H_4)_2Ti]_2$. He proposes that the since the interannular distance between the two bridgehead carbons in the bridged system is considerably shorter than the Van der Waals distance that there is a buildup of charge on bridged ligand system. In the complexes which contain Ti(III) or Ti(IV), the excess electron density can be shifted to the electron-poor titanium; however, Ti(II) is relatively electron-rich and its electron accepting ability is sharply diminished, so no shift in electron density occurs, rendering the complex unstable. Brintzinger found that one ethylene bridged Ti(II) complex is accessible,$(CH_2)_2(C_5H_4)_2Ti(CO)_2$, presumably because the π-accepting ability of the CO ligands stabilizes the excess charge. The dicarbonyl compound was synthesized as shown in Scheme 12a, by treatment of the bridged titanocene dimethyl complex **13** with CO, forming acetone as a side product.[42]

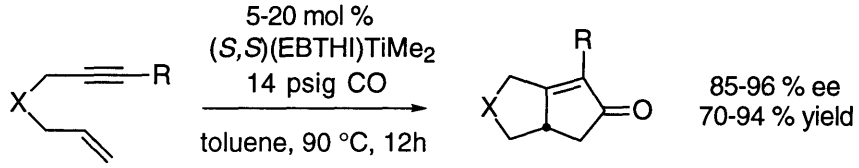
Scheme 12



In an adaptation of the Brintzinger synthesis of $(CH_2)_2(C_5H_4)_2Ti(CO)_2$, we have found that the (*R,R*)(EBTHI)$TiMe_2$ **14** can be transformed in an analogous fashion to (*R,R*)(EBTHI)$Ti(CO)_2$, **15** (Scheme 12b). While **15** was not initially isolated, it was identified by its ^1H NMR spectrum. Subsequently it has been isolated from (EBTHI)$TiCl_2$ by reduction under CO atmosphere.[43]

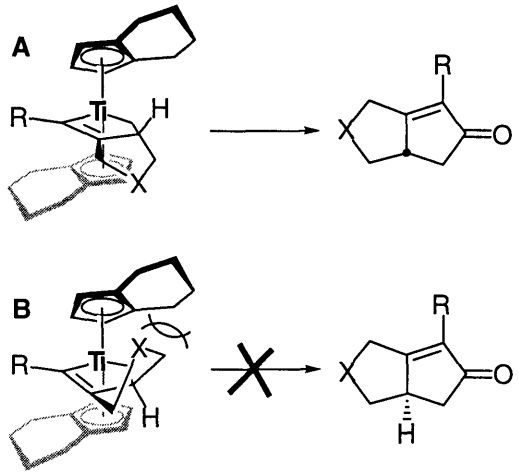
Since we have found that titanocene dicarbonyl is an efficient catalyst for the cyclocarbonylation of enynes as well as enones in a Pauson-Khand-type of methodology,[18] and that we can make the optically active EBTHI analog of the catalyst, the next step became clear. Subsequently, it was discovered in the Buchwald labs by Frederick Hicks that complex **15** (in the (*S,S*) form), generated *in situ* from (*S,S*)(EBTHI)$TiMe_2$, functions as a highly enantioselective catalyst for the conversion of enynes to cyclopentenones.[44] The conditions of this reaction are shown in Scheme 13.

Scheme 13



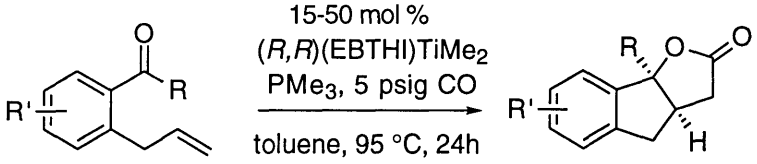
Presumably the enantioselectivity determining step in the enyne cyclocarbonylation reaction involves the relative stabilities of the diastereomeric metallacycles, and two possible metallacycles are shown in Scheme 14 (the ethylene bridge has been omitted for clarity). It is proposed that the diastereoselectivity is dependent on the interaction of the backbone of the enyne substrate with the cyclohexyl ring of the EBTHI ligand. In metallacycle B, there is an unfavorable interaction between the backbone and the ligand; however, metallacycle A suffers from no such interactions, and thus leads to the proposed major enantiomer.

Scheme 14



Since titanocene dicarbonyl is also an effective catalyst for the cyclocarbonylation of *o*-allyl aryl ketones as described herein, we became interested in using the (EBTHI)Ti(CO)$_2$ complex to develop an enantioselective "hetero Pauson-Khand" transformation. Using the (*R,R*)(EBTHI)TiMe$_2$ precatalyst, we found that *o*-allyl aryl ketones can be converted to γ-butyrolactones, but with varying degrees of catalytic efficiency and with ee's varying from excellent to poor. The conditions for the reaction are shown in Scheme 15, and the results are shown in Table 3.[45]

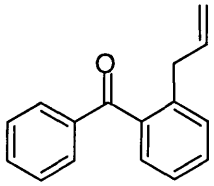
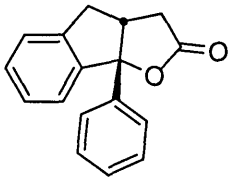
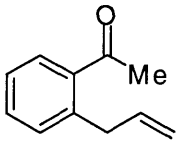
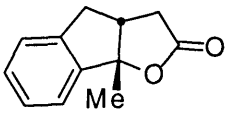
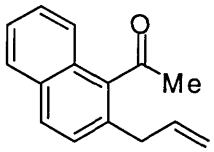
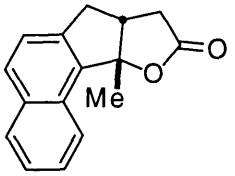
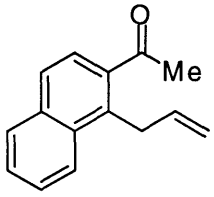
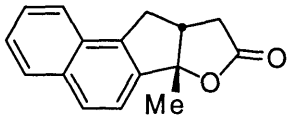
Scheme 15



The substrate in entry 1 is cyclocarbonylated with very high ee, but 50 mol % of the (*R,R*)(EBTHI)TiMe$_2$ reagent is necessary for complete conversion. Additionally, the yield is fairly low, even though no other products are isolated or detected by gas chromatography or ^{1}H NMR. Low yields have been observed in the transformation of other substrates that require large amounts of the substoichiometric titanium reagent (see Scheme 7, Chapter 3). The *o*-allyl napthophenone substrate in entry 3 also requires 50 mol % of the

(*R,R*)(EBTHI)TiMe$_2$ reagent, but in contrast to entry 1, it undergoes nonselective cyclocarbonylation to give a product with an ee of only 5 %. The substrates in entries 2 and 4 are cyclocarbonylated with 15 and 20 mol % of the (*R,R*)(EBTHI)TiMe$_2$ catalyst respectively, but with poor selectivity.

Table 3: Hetero Pauson-Khand reaction utilizing (*R,R*)(EBTHI)TiMe$_2$

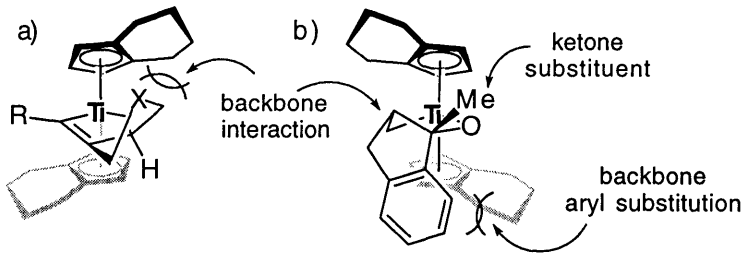
entry	substrate	product	% catalyst	yield (%)	ee (%)
1			50	57	98
2			15	83	27
3			50	62	5
4			20	80	23

In order to rationalize the observed reactivity and enantiomeric excesses in the hetero Pauson-Khand reaction we examined models similar to those proposed in Scheme 14 for the enantioselective catalytic cyclocarbonylation of enynes. There are more steric interactions which need to be considered in the reaction of *o*-allyl aryl ketones: in addition to those involving the backbone of the substrate which presumably dictate the enantioselectivity in the enyne case (Scheme 16a), the substituent on the ketone and the aryl ring fused to the backbone of the substrates can also play a role (Scheme 16b). Therefore, there

are three interactions between the substrate and the EBTHI ligand that dictate the enantioselectivity; depending on the substrate, these interactions can be either reinforcing or conflicting, leading to ee's that vary widely between substrates. Schemes 17 and 18 show the overall analysis for the four substrates listed in Table 3; Scheme 17 is drawn freehand with the unfavorable interactions indicated, and Scheme 18 contains ball and stick models minimized to a first approximation using MacSpartan Plus molecular modeling program.

Examination of the possible metallacycles for entry 2 (Table 3) shows that metallacycle B contains two unfavorable interactions: both the backbone and the methyl ketone substituent interact with the EBTHI ligand. Intermediate A only possesses one unfavorable interaction between the aryl ring in the backbone and the EBTHI ligand, so we believe that this is the favored diastereomer. However, the magnatudes of the interactions are such that there is little energetic difference between these two metallacycles and the ee is low (27 %).

Scheme 16

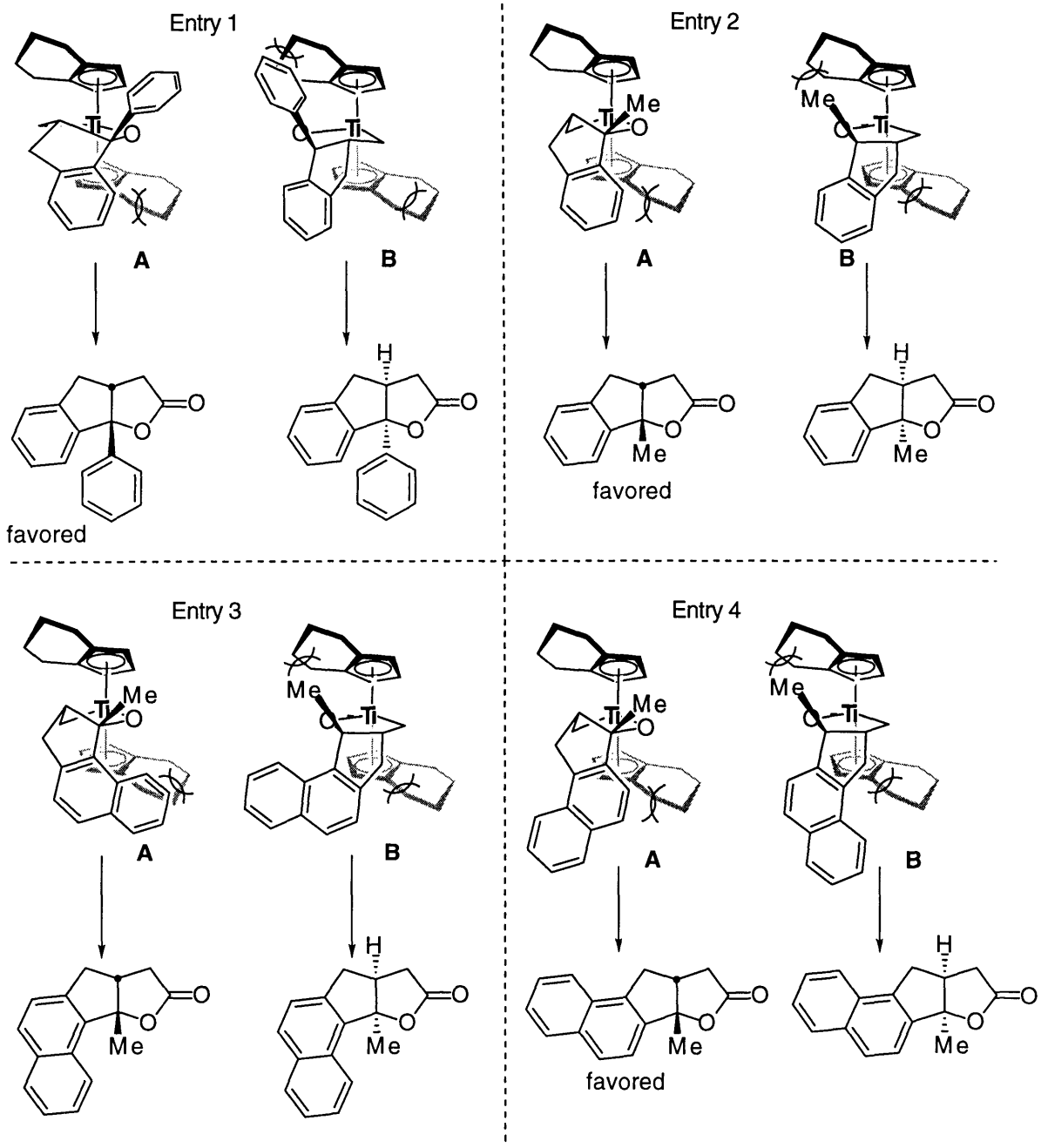


Similarly, the examination of the diastereomers for the cyclocarbonylation of *o*-allyl benzophenone (entry 1) shows that metallacycles A and B contain the same unfavorable interactions as the intermediates for entry 2 discussed above. However, the ketone substituent in this case is a phenyl ring which is larger than the methyl substituent in entry 2, so we postulate that metallacycle B is highly disfavored. Thus the energy difference

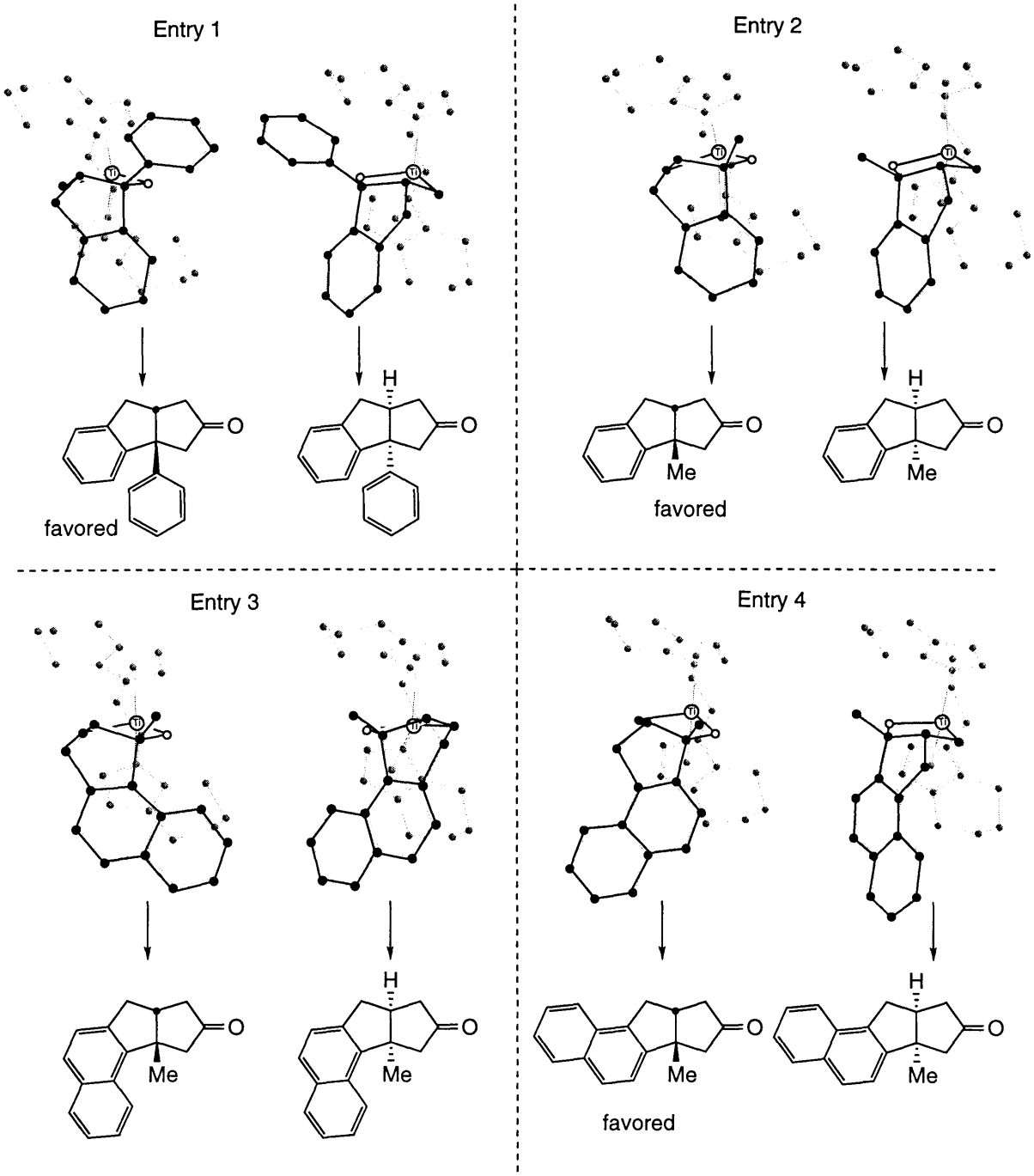
between intermediates A and B is larger than in the acetophenone case (entry 2), so a much higher ee is observed. Both metallacycles are sterically congested, so 50 mol % catalyst is required.

We have also examined the two acetonapthone substrates in entries 3 and 4. The acetonapthone in entry 4 behaves very similarly to *o*-allyl acetophenone in both catalyst efficiency and ee. Examination of the two intermediate metallacycles shows that they are very similar to the *o*-allyl acetophenone case (entry 2) since the second ring of the napthalene is situated in an open quadrant for both intermediates. The cyclization of the *o*-allyl acetonapthone in entry 3, however, produces different results. While the excess bulk of the napthalene structure is situated in an open quadrant in metallacycle B, the napthalene system interacts strongly with the EBTHI ligand in metallacycle A. The ee arises from the energy difference between intermediate B, which contains 2 mildly unfavorable interactions, and intermediate A, which possesses one highly unfavorable interaction. We postulate that the two intermediates are of similar energies, so the resulting product is nearly racemic. As described for entry 1, both of the metallacycles are high in energy, so the substrate in entry 3 requires 50 mol % of the (*R,R*)(EBTHI)$TiMe_2$ reagent for complete conversion to product.

Scheme 17


Entry 1
A
B
favored
Entry 2
Me
A
B
favored
Entry 3
Me
A
B
Me
Entry 4
Me
A
B
favored

Scheme 18


Entry 1
Ti
O
H
favored
Entry 2
Ti
O
Me
favored
H
Me
Entry 3
Ti
Me
O
H
Entry 4
Ti
Me
O
favored
H

Experimental Procedures

General Considerations. All manipulations involving air-sensitive materials were conducted in a Vacuum Atmospheres glovebox under an atmosphere of argon or using standard Schlenk techniques under argon. THF was distilled under argon from sodium/benzophenone ketyl before use. Toluene was distilled under argon from molten sodium, and CH_2Cl_2 was distilled under nitrogen from CaH_2. Pyridine was distilled under argon from CaH_2. Bis(trimethylphosphine)titanocene, $Cp_2Ti(PMe_3)_2$, was prepared from titanocene dichloride (obtained from Boulder Scientific, Boulder, CO) by the procedure of Binger et. al.[46] and was stored in a glovebox under argon. Titanocene dicarbonyl is commercially available from Strem Chemicals, and is also readily synthesized from titanocene dichloride.[47] *Ortho*-allylacetophenone was prepared by a Stille coupling of allyltributyltin and *o*-bromoacetophenone.[48] *Ortho*-iodoacetophenone was synthesized by a modified Sandmeyer procedure.[49] 2-Bromo-4-*t*-butyl-carboxyl-acetophenone was synthesized according to the procedure described by Wakselman.[50] The enone 1,3-diphenyl-5-hexen-1-one and was synthesized by allylation of *trans*-chalcone with allyltrimethylsilane and $TiCl_4$;[51] *cis*/*trans*-1-acetyl-2-allyl cyclohexane was synthesized in a similar manner from 1-acetyl cyclohexene.[22] 2-Iodobenzophenone is commercially available from Trans World Chemicals. All other reagents were available from commercial sources and were used without further purification, unless otherwise noted.

Flash chromatography was performed on E. M. Science Kieselgel 60 (230-400 mesh) unless otherwise noted. Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^1H NMR analysis, and in the cases of unknown compounds, elemental analysis.

Yields indicated in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopies. Previously unreported compounds were also characterized by elemental analysis (E & R Analytical Laboratory, Inc.). Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian XL-500, or a Varian Unity 300. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; qd, quartet of doublets; m, multiplet. All ^{1}H NMR spectra are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer. Gas chromatography (GC) analysis were performed on a Hewlett-Packard 5890 gas chromatograph with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase. Chiral GC analyses were conducted using a 5890 Hewlett-Packard Series II gas chromatograph with an FID detector.

Preparation of the Enone Starting Materials: General Procedure for the Conversion of 2'-Hydroxy Acetophenones into 2'-Allyl Acetophenones: In a dry Schlenk flask, the 2'-hydroxyacetophenone and pyridine (20-30 mL) were combined under argon and cooled to 0 °C. Triflic anhydride was added slowly, and the reaction mixture was allowed to slowly warm to room temperature overnight. The mixture was diluted with diethyl ether (50 mL), washed with 1N aqueous HCl solution (2x 50 mL) followed by brine (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography

and immediately used in the next step. Using an adaptation of Farina's procedure,[52] the triflate, 1.1 equiv allytributyl tin, 0.02 equiv Pd_2dba_3, 0.16 equiv P(2-furyl)$_3$, 3 equiv LiCl (anhydrous), and THF were combined in a dry Schlenk flask fitted with a reflux condenser, and heated to 85 °C for 18 h. The crude reaction mixture was diluted with diethyl ether (50 mL), shaken vigorously with saturated aqueous KF solution (25 mL) for 5 minutes, then washed with brine and dried over $MgSO_4$. Purification by flash chromatography yielded the desired allyl acetophenone.

2'-allyl-5'-methyl acetophenone (Table 1, Entry 2): Using the general procedure, 2'-hydroxy-5'-methyl-acetophenone (2.3 g, 15 mmol) and triflic anhydride (2.8 mL, 17 mmol) were converted to the desired product. Purification by flash chromatography (hexane: diethyl ether = 3: 2) afforded 2.5 g (57 % yield) of a clear oil. The triflate (2.45 g, 8.7 mmol) was reacted with allyl tributyltin (3.23 mL, 10.4 mmol), Pd_2dba_3 (0.16 g, 0.2 mmol), P(2-furyl)$_3$ (0.32 g, 1.4 mmol), LiCl (1.1 g, 26 mmol) and THF (20 mL). The crude product was purified by flash chromatography (hexane: diethyl ether = 9: 1) to afford 1.2 g (79 % yield) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s, 1 H); 7.23 (m, 1 H); 7.16 (d, J = 7.9 Hz, 1 H); 5.96 (m, 1 H); 4.99 (m, 2 H); 3.60 (d, J = 6.4 Hz, 2 H); 2.56 (s, 3 H); 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.3, 138.2, 137.8, 136.7, 135.8, 132.3, 131.3, 129.7, 115.5, 37.7, 29.9, 21.1. IR (neat): 2977, 2921, 1686, 1355, 1267, 1205, 1182, 914, 829 cm^{-1}. Anal. calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.62; H, 8.01.

2'-Allyl-5'-fluoro-acetophenone (Table 1, Entry 3): Using the general procedure, 2'-hydroxy-5'-fluoro-acetophenone (3.1 g, 20 mmol) and triflic anhydride (4.1 mL, 24 mmol) were converted to the desired product. Kugelrohr

distillation followed by recrystallization from CH_2Cl_2 and hexane afforded 3.9 g (68 % yield) of white crystalline material. The triflate (2.8 g, 9.8 mmol) was reacted with allyl tributyltin (3.42 mL, 11 mmol), Pd_2dba_3 (0.179 g, 0.2 mmol), P(2-furyl)$_3$ (0.36 g, 1.5 mmol), LiCl (1.2 g, 28 mmol) and THF (10 mL). The crude product was purified by flash chromatography (hexane: diethyl ether = 19: 1) to afford 0.87 g (50 % yield) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (dd, J = 9.1 Hz, J = 2.7 Hz, 1 H); 7.27 (m, 1 H); 7.12 (td, J = 8.2 Hz, J = 2.7 Hz, 1 H); 5.95 (m, 1 H); 4.99 (m, 2 H); 3.60 (d, J = 6.4 Hz, 2 H); 2.55 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 161.0 (J_F= 245 Hz), 139.6 (J_F= 5.5 Hz), 137.4, 135.4 (J_F= 3.1 Hz), 133.0 (J_F= 7.3 Hz), 118.5 (J_F= 21 Hz), 116.1, 115.8 (J_F= 22 Hz), 37.3, 30.0. IR (neat): 3079, 1694, 1488, 1357, 1262, 1191, 911, 871 cm^{-1}. Anal. calcd for $C_{11}H_{11}FO$: C, 74.14; H, 6.22. Found: C, 74.18; H, 6.25.

2-Allyl benzophenone (Table 1, Entry 4):[48,53] In a dry resealable Schlenk flask, 2-iodobenzophenone (1.0 mL, 5.4 mmol), allyl tributyltin (1.85 mL, 5.9 mmol), palladium tetrakis(triphenylphosphine) (63 mg, 0.054 mmol) and benzene (1 mL) were combined. The reaction mixture was heated to 100 °C for 24 h then cooled to room temperature. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether (10 mL), washed with 10 % aqueous KF solution (10 mL), then dried over $MgSO_4$. The solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (hexane: diethyl ether = 46: 1) to afford 0.9 g (75 % yield) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 7.3 Hz, 2 H); 7.59 (t, J = 7.2 Hz, 1 H); 7.45 (m, 3 H); 7.30 (m, 3 H); 5.88 (m, 1 H); 4.96 (m, 2 H); 3.45 (d, J = 6.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1, 139.2, 139.1, 138.8, 138.0, 137.1, 133.4, 130.6, 130.4, 128.9, 128.6, 125.9, 116.4, 37.7. IR (neat): 3062, 1666, 1597, 1448, 1315, 1269, 925, 703, 638 cm^{-1}.

2'-Allyl-4'-methoxy-acetophenone (Table 1, Entry 5): Using the general procedure, 2'-hydroxy-4'-methoxy-acetophenone (2.5 g, 15 mmol) and triflic anhydride (2.8 mL, 17 mmol) were converted to the desired product. Flash chromatography (hexane: diethyl ether = 3: 2) afforded 2.1 g (47 % yield) of a colorless oil. The triflate (1.5 g, 5.0 mmol) was reacted with allyl tributyltin (1.87 mL, 6.0 mmol), Pd_2dba_3 (0.092 g, 0.1 mmol), P(2-furyl)$_3$ (0.19 g, 0.8 mmol), LiCl (0.64 g, 15 mmol) and THF (10 mL). The crude product was purified by flash chromatography (hexane: diethyl ether = 4: 1) to afford 0.6 g (63 % yield) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 8.2 Hz, 1 H); 6.77 (m, 2 H); 5.98 (m, 1 H); 5.02 (m, 2 H); 3.85 (s, 3 H); 3.72 (d, J = 6.5 Hz, 2 H); 2.54 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 162.2, 143.7, 137.5, 132.6, 130.0, 116.9, 115.8, 110.9, 55.4, 38.8, 29.3. IR (neat): 2974, 1675, 1602, 1567, 1354, 1250, 1134, 1031 cm^{-1}. Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42 Found: C, 75.67; H, 7.32.

2'-Allyl-4'-*t*-butyl carboxyl-acetophenone (Table 1, Entry 6): Using Stille coupling conditions,[48] 2'-bromo-4'-*t*-butyl carboxyl-acetophenone[50] (1.6 g, 5.4 mmol), allyl tributyltin (1.83 mL, 6 mmol), tetrakis(triphenylphosphine) palladium (0.31 g, 0.3 mmol) were combined in a dry sealable Schlenk flask with benzene (3 mL). The reaction was heated to 100 °C for 12 h, then the solvent was removed *in vacuo*. The crude reaction mixture was diluted with diethyl ether (25 mL), washed with H_2O (25 mL), 10 % aq KF solution, and dried over $MgSO_4$. The crude product was purified by flash chromatography (hexane: diethyl ether = 9: 1) to afford 0.91 g (65 % yield) of a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (m, 2 H); 7.62 (d, J = 8.4 Hz, 1 H); 5.97 (m, 1 H); 5.04 (m, 2 H); 3.65 (d, J = 6.4 Hz, 2 H); 2.57 (s, 3 H); 1.60 (s, 9 H). ^{13}C NMR (125

MHz, $CDCl_3$): δ 202.2, 165.0, 141.9, 139.4, 137.0, 134.3, 132.1, 128.4, 127.3, 116.4, 81.7, 37.8, 30.2, 28.3. IR (neat): 2978, 1717, 1702, 1394, 1368, 1356, 1301, 1254, 1166, 1117, 771 cm^{-1}. Anal. calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.86; H, 7.57.

1'-Allyl-2'-acetylnaphthalene (Table 1, Entry 7): Using the general procedure, 1'-hydroxy-2'-acetylnaphthalene (2.8 g, 15 mmol) and triflic anhydride (2.8 mL, 16.5 mmol) were converted to the desired product. Flash chromatography (hexane: diethyl ether = 3: 1) followed by Kugelrohr distillation afforded 1.3 g (27 % yield) of a colorless oil. The triflate (1.27 g, 4 mmol) was reacted with allyl tributyltin (1.49 mL, 4.8 mmol), Pd_2dba_3 (45 m g, 0.05 mmol), P(2-furyl)$_3$ (0.096 g, 0.4 mmol), LiCl (0.51 g, 12 mmol) and THF (5 mL). The crude product was purified by flash chromatography (hexane: diethyl ether = 19: 1) to afford 0.48 g (57 % yield) of a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (m, 1 H); 7.85 (m, 1 H); 7.80 (d, J = 8.5 Hz, 1 H); 7.53 (m, 3 H); 6.09 (m, 1 H); 5.04 (dd, J = 1.8 Hz, J = 24.8 Hz, 1 H); 5.00 (dd, J = 1.6 Hz, J = 31.6 Hz, 1 H); 4.02 (dt, J = 5.9 Hz, J = 1.6 Hz, 2 H); 2.65 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 137.3, 137.2, 135.0, 134.6, 132.5, 128.7, 127.2, 127.1, 126.9, 125.8, 124.2, 116.1, 33.0, 31.1. IR (neat): 3005, 1692, 1468, 1352, 1269, 1235, 814 cm^{-1}. Anal. calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.80; H, 6.54.

2'-Allyl-1'-acetylnaphthalene (Table 1, Entry 8): Using the general procedure, 2'-hydroxy-1'-acetylnaphthalene (2.8 g, 15 mmol) and triflic anhydride (2.8 mL, 16.5 mmol) were converted to the desired product. Flash chromatography (hexane: diethyl ether = 3: 1) followed by Kugelrohr distillation afforded 3.8 g (80 % yield) of a yellow solid. The triflate (1.27 g, 4 mmol) was reacted with allyl tributyltin (1.49 mL, 4.8 mmol), Pd_2dba_3 (45 m g, 0.05 mmol),

$P(2\text{-furyl})_3$ (0.096 g, 0.4 mmol), LiCl (0.51 g, 12 mmol) and THF (5 mL). The crude product was purified by flash chromatography (hexane: diethyl ether = 19: 1) to afford 0.5 g (59 % yield) of a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (m, 2 H); 7.60 (m, 1 H); 7.49 (m, 2 H); 7.35 (d, J = 8.5 Hz, 1 H); 5.98 (m, 1 H); 5.08 (m, 2 H); 3.47 (dt, J = 6.4 Hz, J = 1.6 Hz, 2 H); 2.64 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0, 139.0, 136.6, 132.1, 131.9, 129.1, 129.0, 128.4, 127.8, 127.0, 125.9, 124.2, 116.7, 37.6, 33.5. IR (neat): 3.56, 1698, 1508, 1417, 1351, 1244, 1203, 918, 819, 756 cm^{-1}. Anal. calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.58; H, 6.53.

2'-(3-cyclopentene) acetophenone (Table 1, Entry 10): Using the procedure of Larock,[54] 2-iodo acetophenone (3.05 g, 12.3 mmol), cyclopentene (5.4 mL, 61 mmol), palladium acetate (0.139 g, 0.62 mmol), triphenylphosphine (0.162 g, 0.62 mmol), $(n\text{Bu})_4NCl$ (anhydrous, 3.32 g, 12.3 mmol), KOAc (3.63 g, 37 mmol) and DMF (30 mL) were combined in a dry Schlenk flask fitted with a reflux condenser and heated to 100 °C for 17 h. The reaction mixture was diluted with water and extracted with diethyl ether (3x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (hexane: diethyl ether = 19: 1) to afford 0.58 g (25 % yield) of a colorless oil, which was a 9:1 mixture of the desired product to the isomeric 2'-(4-cyclopentene) acetophenone. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 7.7 Hz, 1 H); 7.39 (m, 1 H); 7.31 (d, J = 6.8 Hz, 1 H); 7.26 (m, 1 H); 5.97 (m, 1 H); 5.81 (m, 1 H); 4.39 (m, 1 H); 2.60 (s, 3 H); 2.56 (m, 2 H); 2.45 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 146.0, 134.3, 132.7, 131.6, 130.0, 128.4, 128.3, 125.9, 47.7, 34.4, 32.6, 30.6. IR (neat): 2849, 1686, 1443, 1356, 1264, 1241,

760, 741, 600 cm^{-1}. Anal. calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.01; H, 7.72.

***O*-allyl-2'-hydroxyacetophenone, 5:**[55] In a dry Schlenk flask under argon, sodium carbonate (2.12 g, 20 mmol), THF (20 mL), DMF (20 mL), and then 2'-hydroxyacetophenone (2.41 mL, 20 mmol) were combined. Allyl bromide (2.60 mL, 30 mmol) was added and the reaction mixture was heated to reflux for 20 h. After cooling to room temperature, the reaction mixture was diluted with diethyl ether (50 mL) and water (50 mL), then extracted with diethyl ether (2x 30 mL). The combined organic layers were then washed with sat. $CuSO_4$ solution (3x 20 mL), 1N aq. NaOH solution (2x 30 mL), and brine, dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude material was purified by flash chromatography (hexane: diethyl ether = 6: 1) to afford 1.4 g (40 % yield) of a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (dd, J = 1.2 Hz, J = 7.6 Hz, 2 H); 7.44 (t, J = 6.6 Hz, 1 H); 6.97 (m, 2 H); 6.10 (m, 1 H); 5.39 (m, 2 H); 4.65 (d, J = 5.3 Hz, 2 H); 2.65 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 158.1, 133.7, 132.8, 130.6, 128.8, 120.9, 118.4, 112.9, 69.6, 32.2. IR (neat): 1674, 1597, 1483, 1450, 1424, 1358, 1294, 1238, 758 cm^{-1}.

General Procedure for the Conversion of Enones to γ-Butyrolactones. Catalyst System A: In an argon-filled glovebox, a dry sealable Schlenk flask was charged with the enone, $Cp_2Ti(PMe_3)_2$, PMe_3 and toluene (2 mL). [Note: the enone was run through a plug of activated alumina in the glovebox and stored under argon. On particularly humid days, the alumina had to be dried under vacuum at 180 °C overnight prior to use to effectively dry the substrate.] The flask was removed from the glovebox, attached to a Schlenk line under Ar, evacuated and backfilled with 18 psig CO.

Caution: Appropriate precautions should be taken when performing reactions under elevated CO pressure. The reaction was heated to 100 °C for 12-18 h. After cooling the reaction mixture to room temperature, the CO was cautiously released in the hood. The crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography.

Catalyst System B: In an argon-filled glovebox, a dry sealable Schlenk flask was charged with the enone, $Cp_2Ti(CO)_2$, PMe_3 and toluene (2 mL). [Note: the enone was run through a plug of activated alumina in the glovebox and stored under argon. On particularly humid days, the alumina had to be dried under vacuum at 180 °C overnight prior to use to effectively dry the substrate.] The flask was removed from the glovebox, attached to a Schlenk line under Ar, evacuated and backfilled with 5 psig CO. **Caution:** Appropriate precautions should be taken when performing reactions under elevated CO pressure. The reaction was heated to 100 °C for 36-48 h. After cooling the reaction mixture to room temperature, the CO was cautiously released in the hood. The crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-2H-indanyl[b]furan-2-one (Table 1, entry 1):** Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (12 mg, 7.5 mol%) and PMe_3 (16 μL, 30 mol%) were used to convert *o*-allylacetophenone (80 mg, 0.50 mmol) to the desired product. Purification by flash chromatography (hexane: diethyl ether = 1:1) yielded 86 mg (91 % yield) of a clear colorless oil. Using catalyst system B, $Cp_2Ti(CO)_2$ (9 mg, 7.5 mol%) and PMe_3 (16 μL, 30 mol%) were used to convert *o*-allylacetophenone (80 mg, 0.50 mmol) to 90 mg (96 % yield) of the desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (m, 1 H); 7.28

(m, 3 H); 3.31 (dd, J = 7.1 Hz, J = 16.5 Hz, 1 H); 2.95 (m, 2 H); 2.83 (dd, J = 2.0 Hz, J = 16.45 Hz, 1 H); 2.40 (m, 1 H); 1.74 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 142.5, 141.1, 129.6, 127.6, 125.3, 124.2, 95.4, 44.2, 36.9, 36.6, 25.0. IR (neat): 2929, 1766, 1442, 1379, 1206, 1066, 954, 768 cm^{-1}. Anal. calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.36; H, 6.54.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-4'-methyl-2H-indanyl[b]furan-2-one (Table 1, Entry 2):** Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (16 mg, 10 mol%) was used to convert 2'-allyl-5'-methylacetophenone (87 mg, 0.50 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl ether = 1: 1) yielded 90 mg (89 % yield) of a white solid. Using catalyst system B, $Cp_2Ti(CO)_2$ (9 mg, 7.5 mol%) and PMe_3 (16 μL, 30 mol%) were used to convert 2'-allyl-5'-methylacetophenone (87 mg, 0.50 mmol) to 87 mg (87 % yield) of the desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (s, 1 H); 7.13 (m, 2 H); 3.25 (dd, J = 7 Hz, J = 16.5 Hz; 1 H); 2.95 (m, 2 H); 2.77 (dd, J = 2.4 Hz, J = 16.5 Hz, 1 H); 2.38 (m, 1 H); 2.36 (s, 3 H), 1.72 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 133.7, 129.1, 128.6, 121.7, 116.2, 115.8, 86.5, 35.6, 27.8, 27.6, 16.1, 12.4. IR (KBr): 2918, 2847, 1751, 1493, 1310, 1242, 1208, 1147, 1069, 936, 858, 810. Mp = 82 - 84°C. Anal. calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.20; H, 7.18.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-4'-Fluoro-2H-indanyl[b]furan-2-one (Table 1, Entry 3):** $Cp_2Ti(PMe_3)_2$ (16 mg, 10 mol%) and PMe_3 (20 μL, 40 mol%) were used to convert 5-fluoro-*o*-allylacetophenone (89 mg, 0.5 mmol) to the desired product. Purification by flash chromatography (hexane: diethyl ether = 1: 1) afforded 82 mg (80 % yield) of a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 1 H); 7.08 (m, 3 H); 3.27 (dd, J = 6.8 Hz, J = 15.6 Hz, 1 H);

2.95 (m, 2 H); 2.79 (d, J = 16.5 Hz, 1 H); 2.41 (m, 1 H); 1.72 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 162.8 (J_F= 244 Hz), 144.7 (J_F= 8 Hz), 136.5, 126.8 (J_F= 8 Hz), 117.2 (J_F= 23 Hz), 111.2 (J_F= 22 Hz), 95.0, 45.0, 36.7, 36.4, 25.1. IR (neat): 2972, 1769, 1599, 1487, 1307, 1257, 1202, 1187, 925, 817 cm^{-1}. Anal. calcd for $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38. Found: C, 69.73; H, 5.25.

***cis*-2,3,4,6a-Tetrahydro-6a-phenyl-2H-indanyl[b]furan-2-one (Table 1, Entry 4):** $Cp_2Ti(PMe_3)_2$ (9 mg, 5 mol%) and PMe_3 (11 μL, 20 mol%) were used to convert *o*-allyl-benzophenone (116 mg, 0.52 mmol) to the desired product. Purification by flash chromatography (hexane: diethyl ether = 1: 1) afforded 110 mg (97 % yield) of a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 8 H); 7.17 (d, J = 7.7 Hz, 1 H); 3.47 (dd, J = 8.1 Hz, J = 16.5 Hz, 1 H); 3.25 (m, 1 H); 2.95 (m, 2 H); 2.51 (dd, J = 5.2 Hz, J = 18.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 142.8, 142.7, 143.3, 130.0, 128.7 (2), 128.1, 126.3, 125.3, 125.2, 98.5, 47.5, 37.7, 36.6. IR (neat): 3028, 1769, 1448, 1231, 1189, 1146, 1001, 976, 754, 700 cm^{-1}. Anal. calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.73; H, 5.80.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-3'-methoxy-2H-indanyl[b]furan-2-one (Table 1, Entry 5):** Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (33 mg, 20 mol%) and PMe_3 (33 μL, 60 mol%) were used to convert 4'-methoxy-6'-allylacetophenone (95 mg, 0.50 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl ether = 1: 1) yielded 80 mg (74 % yield) of a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, J = 8.4 Hz, 1 H); 6.83 (dd, J = 8.5 Hz, J = 2.4 Hz, 1 H); 6.74 (d, J = 2.3 Hz, 1 H); 3.80 (s, 3 H); 3.27 (dd, J = 7.5 Hz, J = 16.6 Hz, 1 H); 2.95 (m, 2 H); 2.78 (dd, J = 3.3 Hz, J = 16.5 Hz, 1 H); 2.43 (m, 1 H); 1.71 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 161.6, 143.4,

135.2, 125.3, 114.4, 110.2, 95.2, 55.7, 44.9, 37.4, 36.9, 25.3. IR (KBr): 1750, 1503, 1305, 1243, 1138, 1064, 913, 837 Mp = 73 - 75 °C. Anal. calcd for $C_{13}H_{14}O_3$: C, 71.54; H,6.47. Found: C, 71.63; H, 6.63.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-3'-*t*-butyl-carboxylate-2H-indanyl[b]furan-2-one (Table 1, Entry 6):** Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (10 mg, 7.5 mol%) and PMe_3 (12 μL, 30 mol%) were used to convert 4'-*t*-butyl-carboxylate-6'-allylacetophenone (130 mg, 0.50 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl ether = 1: 1) yielded 136 mg (93 % yield) of a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 8.0 Hz, 1 H); 7.87 (s, 1 H); 7.45 (d, J = 8.0 Hz, 1 H); 3.33 (dd, J = 7.5 Hz, J = 16.5 Hz, 1 H); 2.97 (m, 2 H); 2.87 (d, J = 16.8 Hz, 1 H); 2.39 (m, 1 H); 1.73 (s, 3 H); 1.59 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 165.5, 147.0, 141.3, 134.1, 129.4, 126.8, 124.3, 94.7, 81.5, 44.8, 36.9, 36.7, 28.4, 25.2. IR (KBr): 2971, 1758, 1708, 1458, 1417, 1335, 1298, 1169, 1095, 955, 772 cm^{-1}. Mp = 95 - 97 °C. Anal. calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 71.02; H, 7.21.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-1',2'-benzo-2H-indanyl[b]furan-2-one (Table 1, Entry 7):** Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (16 mg, 10 mol%) and PMe_3 (20 μL, 40 mol%) were used to convert 1'-allyl-2'-acetyl-napthalene (100 mg, 0.48 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl ether = 1: 1) yielded 97 mg (87 % yield) of a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (m, 1 H); 7.82 (m, 2 H); 7.54 (m, 3 H); 3.62 (dd, J = 7.5 Hz, J = 17.0 Hz, 1 H); 3.19 (m, 2 H); 3.10 (m, 1 H); 2.50 (dd, J = 4.9 Hz, J = 17.1 Hz, 1 H); 1.82 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 139.6, 137.6, 134.,3, 130.3, 128.9, 128.8, 126.8, 126.7, 124.6,

121.5, 96.5, 44.1, 37.3, 35.8, 25.4. IR (KBr): 2968, 1760, 1296, 1229, 1141, 1065, 916, 811, 756 cm^{-1} Mp = 131 - 134 °C. Anal. calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.89; H, 6.13.

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-3',4'-benzo-2H-indanyl[b]furan-2-one (Table 1, Entry 8):** Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (12 mg, 7.5 mol%) and PMe_3 (15 μL, 30 mol%) were used to convert 1'-acetyl-2'-allyl-napthalene (100 mg, 0.48 mmol) to the desired product. Purification by flash chromatography (hexane: ethyl ether = 1: 1) yielded 103 mg (92 % yield) of a white solid. Using catalyst system B, $Cp_2Ti(CO)_2$ (6 mg, 7.5 mol%) and PMe_3 (11 μL, 30 mol%) were used to convert 1'-acetyl-2'-allyl-napthalene (75 mg, 0.36 mmol) to 78 mg (93 % yield) of the desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.4 Hz, 1 H); 7.85 (dd, *J* = 8.0 Hz, *J* = 17.0 Hz, 2 H); 7.52 (m, 2 H); 7.34 (d, *J* = 8.4 Hz, 1 H); 3.39 (dd, *J* = 6.7 Hz, *J* = 16.5 Hz, 1 H); 3.01 (m, 3 H); 2.37 (dd, *J* = 7.5 Hz, *J* = 16.3 Hz, 1 H); 1.94 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ176.4, 137.8, 137.2, 133.8, 130.8, 129.6, 129.8, 127.1, 125.9, 124.3, 123.5, 97.1, 45.7, 37.1, 36.5, 25.6. IR (KBr): 1766, 1412, 1250, 1211, 1093, 955, 938, 812, 752 cm^{-1}. Mp = 103 - 106 °C. Anal. calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.78; H, 6.04.

***cis*-Hexahydro-6a-phenyl-5-*endo*-phenyl-2H-cyclopenta[b]furan-2-one (Table 1, Entry 9):** Using catalyst system B, $Cp_2Ti(CO)_2$ (23 mg, 20 mol%) and PMe_3 (51 μL, 1 equiv) were used to convert 1,3-diphenyl-5-hexen-2-one (0.125 g, 0.5 mmol) to the desired product. Purification by flash chromatography (hexane: diethyl ether = 9: 1) yielded 120 mg (86 % yield) of an 14:1 mixture of diastereomers of a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 10 H); 3.53 (m, 1 H); 2.97 (m, 1 H); 2.4-2.8 (m, 5 H); 1.83 (q, *J* = 12.4

Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 143.9, 142.2, 128.7, 128.7, 127.7, 126.9, 126.8, 123.9, 96.2, 49.6, 48.5, 46.0, 41.3, 34.1. IR (KBr): 3026, 2966, 1775, 1600, 1452, 1179, 970, 699 cm^{-1}. Mp = 89-91 °C. Anal. calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.80; H, 6.39.

Table 1, Entry 10: Using catalyst system A, $Cp_2Ti(PMe_3)_2$ (8 mg, 10 mol%) and PMe_3 (10 μL, 40 mol%) were used to convert 2'-(3-cyclopentene) acetophenone (47 mg, 0.25 mmol) to the desired product. The starting enone was contaminated with approx. 9 % of the isomeric 2'-(4-cyclopentene) acetophenone, which was carried through the reaction and recovered unchanged. Purification by flash chromatography (hexane: diethyl ether = 3: 2) yielded 44 mg (82 % yield) of a colorless oil. Using catalyst system B, $Cp_2Ti(CO)_2$ (6 mg, 5 mol%) and PMe_3 (10 μL, 20 mol%) were used to convert 2'-(3-cyclopentene) acetophenone (93 mg, 0.5 mmol) to 88 mg (82% yield) of the desired product. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 3 H); 7.22 (d, J = 6.5 Hz, 1 H); 3.81 (dd, J = 7.4 Hz, J = 13.1 Hz, 1 H); 3.37 (t, J = 9.7 Hz, 1 H); 3.25 (m, 1 H); 2.13 (m, 2 H); 1.89 (m, 1 H); 1.78 (s, 3 H); 1.74 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.5, 145.9, 143.5, 130.2, 128.0, 124.8, 124.3, 93.5, 56.1, 50.0, 47.1, 35.0, 32.1, 26.4. IR (neat): 2965, 1758, 1223, 1145, 1129, 1064, 761 cm^{-1}. Anal. calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.51; H, 6.62.

Compound 6: Using general procedure B, $Cp_2Ti(CO)_2$ (59 mg, 0.25 mmol) and PMe_3 (52 μL, 1 equiv) were used to convert *o*-allyl-2'-hydroxyacetophenone (88 mg, 0.5 mmol) to the desired product. Purification by flash chromatography (hexane: diethyl ether = 3: 2) yielded 44 mg (43 % yield) of the a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (dd, J = 1.6 Hz, J =

7.8 Hz, 1 H); 7.22 (td, J = 1.6 Hz, J = 6.7 Hz, 1 H); 7.02 (dd, J = 1.1 Hz, J = 8.0 Hz, 1 H); 6.87 (dd, J = 1.1 Hz, J = 8.3 Hz, 1 H); 4.19 (m, 1 H); 4.10 (dd, J = 10.4 Hz, J = 2.6 Hz, 1 H); 2.71 (m, 3 H); 1.82 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 153.4, 130.2, 129.0, 124.0, 122.5, 117.4, 81.2, 64.3, 41.3, 31.1, 28.5. IR (neat): 2977, 1770, 1488, 1306, 1230, 1129, 944, 762 cm^{-1}. Anal. calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.49; H, 5.99.

Compound 8: In an argon filled glovebox, a dry sealable Schlenk flask was charged with *cis/trans*-1-acetyl-2-allyl cyclohexane (83 mg, 0.5 mmol), $Cp_2Ti(PMe_3)_2$ (182 mg, 0.55 mmol), and toluene (2 mL). The flask was removed from the glovebox, evacuated, backfilled with 12 psig CO and heated to 70 °C for 15 h. After cooling to room temperature, the crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and the solvent was removed *in vacuo* to afford the crude product. Purification by flash chromatography (hexane: diethyl ether = 4: 1) yielded 42 mg (42 % yield) of a 5: 1: 1 mixture of diastereomers. In one case, the major isomer was obtained for characterization in 90 % diasteromeric purity by flash chromatography. ^1H NMR (500 MHz, $CDCl_3$, major isomer): δ 2.87 (dd, J = 10.7 Hz, J = 18.6 Hz, 1 H); 2.34 (dd, J = 4.4 Hz, J = 18.6 Hz, 1 H); 2.30 (m, 1 H); 2.18 (m, 1 H); 1.91 (m, 2 H); 1.81 (d, J = 15.0 Hz, 1 H); 1.74 (d, J = 15.0 Hz, 1 H); 1.37 (td, J = 15.0 Hz, J = 2.9 Hz, 1 H); 1.28 (s, 3 H); 1.0 - 1.6 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$, major isomer): δ 176.9, 94.6, 55.4, 43.7, 43.1, 39.7, 36.7, 32.1, 26.7, 26.0, 25.9, 22.5. IR (neat, mixture): 2925, 2853, 1766, 1260, 1125, 1022, 950 cm^{-1}. Anal. calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.04; H, 9.28.

Relative Rate Determination: The relative rates were determined by running a competition reaction of 0.26 mmol of aryl-ketone against *o*-

allylacetophenone except in the case of *o*-allylbenzophenone, which was run against 4'-*t*-butyl-carboxylate-6'-allylacetophenone. Generally, in an argon-filled glovebox, a dry sealable Schlenk flask was charged with the 0.25 mmol enone, *o*-allylacetophenone (41 mg, 0.26 mmol), $Cp_2Ti(CO)_2$ (3 mg, 0.013 mmol) PMe_3 (5 μL, 0.05 mmol), biphenyl as an internal standard (8 mg, 0.05 mmol) and toluene (1 mL). The flask was removed from the glovebox, attached to a Schlenk line under Ar, evacuated and backfilled with 5 psig CO. **Caution:** Appropriate precautions should be taken when performing reactions under elevated CO pressure. The reaction was heated to 100 °C for 1-5 h (the reacion was allowed to proceed to less than 10 % conversion of the faster enone). After cooling the reaction mixture to room temperature, the CO was cautiously released in the hood. The crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether, and the relative concentrations of the products were analyzed by GC against the internal standard.

Hammett Analysis: The Hammett plot in Figure 1 was derived from the numbers shown in Table 4,[56] and the error analysis was derived as shown below.

Table 4: Data for the Hammett plot in Figure 1.

entry (from table 2)	relative rate	σ_p or σ_m	log(rate)	deviation (from theoretical line)
2	5.64	0.44	0.75	0.03
3	3.91	0.34	0.59	0.01
4	1	0	0	0.09
5	0.66	-0.12	-0.43	0.03
6	0.36	-0.06	-0.18	0.1

Error analysis (for the slope of the line in Figure 1):[57]

$$\Sigma x = 0.73 \qquad \Sigma x^2 = 0.33 \qquad S_y^2 = \frac{\Sigma d^2}{N - 1}$$
$$(\Sigma x)^2 = 0.53 \qquad \Sigma d^2 = 0.02$$

$$S_m = \left[\frac{S_y^2}{\Sigma x^2 - \frac{(\Sigma x)^2}{N}} \right]^{1/2} = \left[\frac{0.005}{0.33 - 0.11} \right]^{1/2} = 0.15$$

d = Y deviation = Y(actual) - Y(theoretical)
S_y = standard deviation of residuals
S_m = standard deviation of slope

Determination of Enantiomeric Purity. The enantiomeric excesses (% ee) were determined by chiral GC analysis. A Chiraldex G-TA 20 m x 0.25 mm (ASTEC) capillary column was used.

Dimethyl (*R,R*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium. To a Schlenk flask under argon were added (*R,R,R*)-(EBTHI)Ti(BINOL)[58] (2.0 g, 3.4 mmol) and Et_2O (100 mL), and the flask was cooled to -78 °C. MeLi (15 mL of 1.4 M in diethyl ether (no LiBr), 19.0 mmol) was added slowly, and the reaction mixture was allowed to warm to room temperature and stir for 4 hours. The solvent was removed *in vacuo*, and the crude product was taken into the glovebox. The product was dissolved in pentane (50 mL) and filtered through a plug of Celite, followed by rinsing with pentane. The solvent was removed *in vacuo* to yield 980 mg (86% yield) of the desired product as yellow-orange crystals.[59]

(*R,R*)-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dicarbonyl: ^{1}H NMR spectral identification. The title compound was synthesized *in situ* from dimethyl (*R,R*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-

indenyl)titanium under CO pressure (5 psig) and was not isolated. However, it was identified by ^{1}H NMR spectroscopy: ^{1}H NMR (300 MHz, C_6D_6): δ 4.74 (d, *J* = 2.4 Hz, 2 H); 4.30 (d, *J* = 2.4 Hz, 2 H); 2.24 (m, 8 H); 1.78 (m, 4 H); 1.51 (m, 8 H).

General Procedure for the Asymmetric Conversion of Enones to γ–Butyrolactones. In an argon filled glovebox, a dry sealable Schlenk flask was charged with (*R,R*)-(EBTHI)$TiMe_2$, toluene (2 mL), PMe_3 and the substrate. The Schlenk flask was removed from the glovebox, evacuated and backfilled with 5 psig CO. **Caution:** Appropriate precautions should be taken when performing reactions under elevated CO pressure. The reaction was heated to 95 °C for 24 h. After cooling the reaction mixture to room temperature, the CO was cautiously released in the hood. In the air, the crude reaction mixture was filtered through a plug of silica gel with the aid of diethyl ether and purified by flash chromatography. **Note:** All substrates were passed through a plug of alumina in the glovebox prior to reaction to remove adventitious moisture. On particularly humid days, the alumina had to be dried under vacuum at 180 °C overnight prior to use to effectively dry the substrate.

***cis*-2,3,4,6a-Tetrahydro-6a-phenyl-2H-indanyl[b]furan-2-one (Table 3, Entry 1):** The general procedure employing 0.18 mmol (64 mg) (*R,R*)-(EBTHI)$TiMe_2$ and 0.35 mmol (36 μL) PMe_3 was used to convert *o*-allylbenzophenone (78 mg, 0.35 mmol) to the desired product. Purification by flash chromatography (hexane:ether = 1:1) afforded 50 mg (83 % yield) of a white solid. The ee was determined to be 99 %. Mp = 118-120 °C. The ^{1}H NMR spectrum matched the published spectrum (see above).

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-2H-indanyl[b]furan-2-one (Table 3, entry 2):** The general procedure employing 0.08 mmol (26 mg) (*R,R*)-(EBTHI)$TiMe_2$ and 0.16 mmol (16 μL) PMe_3 was used to convert *o*-allylacetophenone (80 mg, 0.50 mmol) to the desired product. Purification by flash chromatography (hexane:ether = 1:1) afforded 78 mg (83 % yield) of a clear oil. The ee was determined to be 29 %. The ^1H NMR spectrum matched the published spectrum (see above).

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-3',4'-benzo-2H-indanyl[b]furan-2-one (Table 3, Entry 3):** The general procedure employing 0.18 mmol (65 mg) (*R,R*)-(EBTHI)$TiMe_2$ and 0.35 mmol (36 μL) PMe_3 was used to convert 1'-acetyl-2'-allyl-napthalene (74 mg, 0.35 mmol) to the desired product. Purification by flash chromatography (hexane:ether = 1:1) afforded 52 mg (63 % yield) of a white solid. The ee was determined to be 4 %. Mp = 79 - 80 °C. The ^1H NMR spectrum matched the published spectrum (see above).

***cis*-2,3,4,6a-Tetrahydro-6a-methyl-1',2'-benzo-2H-indanyl[b]furan-2-one (Table 3, Entry 4):** The general procedure employing 0.08 mmol (28 mg) (*R,R*)-(EBTHI)$TiMe_2$ and 0.16 mmol (16 μL) PMe_3 was used to convert 1'-allyl-2'-acetyl-napthalene (80 mg, 0.38 mmol) to the desired product. Purification by flash chromatography (hexane:ether = 1:1) afforded 75 mg (83 % yield) of a white solid. The ee was determined to be 23 %. Mp = 125 - 128 °C. The ^1H NMR spectrum matched the published spectrum (see above).

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