DEVELOPMENT OF NOVEL TITANIUM-CATALYZED ORGANIC TRANSFORMATIONS

by

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Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

May 1994

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ABSTRACT

A new titanium-catalyzed hydrosilylation of esters is described. The procedure is experimentally simple and efficient, and uses inexpensive materials to convert esters into the corresponding primary alcohols. The reaction also displays a moderate level of tolerance toward other easily reducible organic functional groups such as olefins, epoxides and halides. A modification of the reaction conditions is described in which five- and six-membered-ring lactones are converted to the corresponding lactols in high yields.

A second-generation catalyst system is presented which cleanly hydrosilylates esters to silyl ethers at 40-55 °C. These intermediates can be easily converted to the corresponding primary alcohols via aqueous acid or alkaline hydrolysis in excellent overall yield. The reaction is catalyzed by several early transition-metal alkoxides. It can be carried out in the air, without solvent, and displays a high level of functional group compatibility.

The first early transition-metal catalyzed enyne cyclization reaction is described. The system converts enyne substrates to bicyclic iminocyclopentenes through the use of 10 mol % of $Cp_2Ti(PMe_3)_2$ in the presence of a silyl cyanide. Subsequent hydrolysis produces the corresponding bicyclic cyclopentenones in good overall yield. The cyclization reaction is tolerant of polar function groups such as ethers, amines, and esters and is diastereoselective for certain chiral enyne substrates.

Thesis Supervisor: Professor Stephen L. Buchwald
Title: Professor of Chemistry

ACKNOWLEDGMENTS

I want to take this opportunity to acknowledge a few people who share responsibility for my choice of a career in chemistry. My parents started me down the path, perhaps unwittingly, by purchasing a "Mr. Wizard's Chemistry Set" as a Chanukah present for me when I was about eight years old. To this day, it gives me great pride to know that, using the series of tests described in the booklet, I correctly identified the "Mystery Powder" (it was a mixture of sucrose and acetylsalicylic acid, aka sugar and aspirin).

I was also lucky enough to have "Doc" Edwin VanDam as my high school chemistry instructor for two years. His enthusiasm and love of science first got me thinking about chemistry as a career and not just a passing interest. He was always willing to discuss opportunities in chemistry with me, and, with his cries of "SCIENCE!" was a true inspiration to his students. He also helped me perform my first organic reaction, an esterification of salicylic acid to form methyl salicylate (oil of wintergreen).

I entered college as a pre-med major, but one of the major reasons I left as a chemist was Dr. Paul Knochel, an excellent mentor and role model. Paul's enthusiasm was completely contagious. "Chemical research is like a game to me," he said, "and the amazing things is, people will pay me to play it!" Thank you, Paul, for teaching me the rules of a game I hope to play happily for a very long time.

My research advisor, Dr. Stephen Buchwald, deserves recognition for all his help along the way. He took the time to speak to me about graduate school when I was an undergraduate, and he was instrumental in my decision to attend MIT. I also thank him for constantly challenging me to make my reactions faster, cheaper, and safer, and for creating a group environment which fostered teamwork and openness in a field sometimes plagued with too much competition. Also, I never would have met my wife, Kathryn Cannon, if Steve had not hired her as his secretary. Thanks, Steve!

I would like to acknowledge past and present members of the Buchwald group, especially members of "Team Titanium", for their helpful discussions, ideas, and general assistance over the years. Alberto Gutiérrez is the unsung hero of the titanium project and deserves special recognition for his incredibly insightful comments and suggestions. Many thanks are also in order for Chris Willoughby, Mary Beth Carter, Peter Petillo, Natasha Kablaoui, and Fred Hicks, who read and corrected this document in record time.

I was privileged to work with two undergraduate research associates during my tenure at MIT. Many thanks to Lori Yerkey and Andrew Tseng who helped synthesize many of the enyne substrates used in Chapter 2. Lori also worked on her own carbonyl reduction project: the reduction of cyclic imides to pyrroles. Best of luck to both of you in the future. I hope I was able to enrich your undergraduate experience a bit.

Finally, I am deeply indebted to my wife, Kathryn Cannon, who, aside from putting up with me on more or less a daily basis for the past two and a half years, went above and beyond the call of duty during the thesis-writing crunch by bringing me dinner, finding and photocopying references, and providing tons of emotional support throughout the whole ordeal.

DEDICATION

The Past: Dedicated to the memory of Michael Joseph Kaplan (October 29, 1967 - March 5, 1988), best friend and fellow scientist, whose life was cut short well before its time by a drunk driver. I miss his energy, his intelligence, and his humor, and there will always be an empty space in my heart where he used to be.

The Future: For Kathy, a very special person with whom I am incredibly excited to explore life's great pageant. This is just one of many new beginnings.

PREFACE

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

Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. "A Catalytic Method for the Reduction of Esters to Alcohols", *J. Am. Chem. Soc.* **1991**, *113*, 5093.

Buchwald, S. L.; Kreutzer, K. A.; Gutiérrez, A.; Berk, S. C. "Catalytic Reduction of Organic Carbonyls Using Metal Catalysts", *U.S. Patent App. Ser. #792,233*, 1991.

Berk, S. C.; Buchwald, S. L. "An Air-Stable Catalyst System for the Reduction Of Esters To Alcohols", *J. Org. Chem.* **1992**, *57*, 3751 and *ibid.* **1993**, *58*, 3221.

Berk, S. C.; Grossman, R. B.; Buchwald, S. L. "Titanocene-catalyzed Conversion of Enynes to Bicyclic Cyclopentenones", *J. Am. Chem. Soc.* **1993**, *115*, 4912.

Barr, K. J.; Berk, S. C; Buchwald, S. L. "Titanocene-Catalyzed Reduction of Esters Using Polymethylhydrosiloxane as the Stoichiometric Reductant", Manuscript in preparation.

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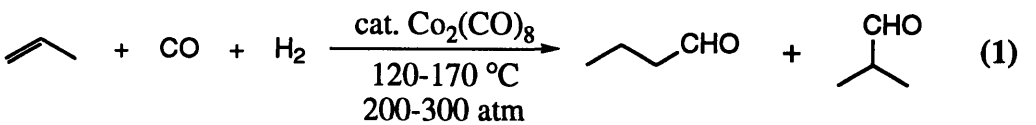
ABBREVIATIONS

Cp	η^5-cyclopentadienyl
d	doublet
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMPU	dimethylpropyleneurea
DMSO	dimethylsulfoxide
EBTHI	η^5-4,5,6,7-ethylene-1,2-bis(tetrahydroindenyl)
equiv	equivalent(s)
GC	gas chromatography
h	hour(s)
HRMS	high resolution mass spectroscopy
IR	infrared
min	minute(s)
NMR	nuclear magnetic resonance
PMHS	polymethylhydrosiloxane
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
quint	quintet
r.t.	room temperature
s	singlet
sat. aq.	saturated aqueous
t	triplet
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl

INTRODUCTION

The past 60 years have seen organometallic chemistry emerge from its infancy to become a powerful method for discovering novel organic transformations. As the field has matured, its major challenges have grown from the study of new reactivity ("What can we do?") to include the refinement of these discoveries into efficient and practicable synthetic organic methods ("How can we do it better?"). To this end, a tremendous amount of effort has gone into the development of metal-mediated organic transformations which would proceed under the mildest possible conditions, and which would ideally utilize a catalytic amount of the metal complex. Aside from simply reducing the cost of materials and the amount of metal waste generated in the reaction, catalysis lends itself to the development of both large scale continuous flow processes and reagent-controlled asymmetric synthesis. In the latter, a small amount of an enantiopure organometallic compound may be used to convert hundreds of equivalents of prochiral substrates into useful enantiopure products. For this reason, the rational design and development of such metal-mediated catalytic cycles now stands in the forefront of interest in the field of organometallic chemistry. Some of the important advances that have been achieved in this area over the past several decades include:

- The evolution of the hydroformylation reaction from a high temperature, high pressure process[1a] (eq 1) to a low pressure variant which proceeds at 60°C, can tolerate a wide range of functional groups and is highly regiospecific[1b] (eq 2).



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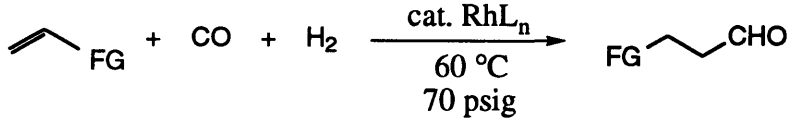
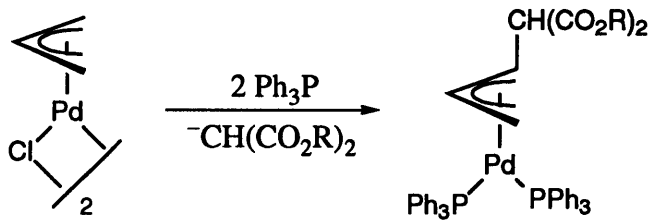


(2)

FG includes: ketone, ester, acid, amide, nitrile, halide, alcohol, ether, acetal, thioacetal, imide
L_n = a specialized bis-organophosphite ligand

• The development of stoichiometric reactions of η^3-allyl complexes of palladium[2a] (eq 3) into the palladium(0)-catalyzed nucleophilic substitution reaction of allylic compounds,[2b] (eq 4) which is now widely used in the synthetic organic community.



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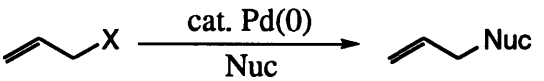
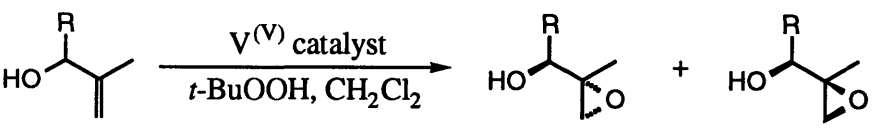


(4)

X = OAc, O_2CR, OCO_2R, OPh, OH, NR_2, SO_2Ph, NO_2, epoxide

• The development of the vanadium-catalyzed stereoselective epoxidation reaction[3a] (eq 5) into the now famous titanium-catalyzed asymmetric epoxidation process[3b] (eq 6). Although not technically an organometallic reaction, the discovery and optimization of this process still stands as an example of the application of intuition and mechanistic insight into developing workable catalytic cycles.



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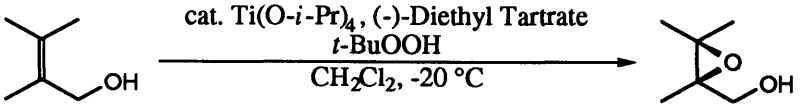

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The discovery of new metal-mediated organic reactions and their design and development into general and workable methods for organic synthesis is one of the major

aims of research in the Buchwald group. In particular, the work presented in this thesis focuses on three novel catalytic transformations mediated by organotitanium reagents. Chapter 1 discusses the development of ester reduction catalyst systems. The first generation catalyst, presented in Chapter 1, Part 1, grew out of the discovery of an interesting titanium-catalyzed silane disproportionation reaction. Based on several mechanistic assumptions about this new process, we were able to design a mild and efficient carbonyl reduction system. Through analysis of the proposed catalytic cycle, we have succeeded in modifying the conditions of this reaction to reduce lactones to the corresponding lactols. We have also exploited the mechanistic model of the reaction to design an air-stable, second generation catalyst system. Chapter 1, Part 2 describes this ester reduction system, which displays a greater functional group tolerance, is more efficient in most cases, and can be run without solvent. Chapter 2 presents the first early transition metal-catalyzed enyne cyclization reaction to produce bicyclic cyclopentenones. In this case, the catalytic cycle was constructed via the marriage of several key results from studies of stoichiometric, titanium-mediated processes such as reductive cyclization, isocyanide insertion and reductive elimination.

For each of these transformations, novel reactivity was first discovered, followed by a mechanism-based approach to the construction of a workable catalytic cycle. An additional guiding principle of this research was its applicability to organic synthesis. Thus, issues such as experimental simplicity, high yields, reproducibility, and safety were of utmost importance in the design and implementation of the processes presented herein. This rational, applications-oriented approach has been quite successful in providing the novel reactions described herein, and will hopefully offer new tools to the synthetic chemist.

CHAPTER 1

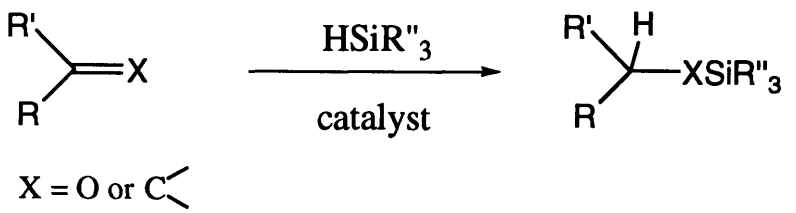
DEVELOPMENT OF TITANIUM-CATALYZED ESTER REDUCTION REACTIONS

Part 1. The Cp_2TiCl_2 / 2 *n*-BuLi Reduction System

Background

Carbonyl reduction reactions are an important class of transformations which, taken together with the myriad of other functional group manipulation reactions, make up the "tool chest" of the synthetic organic chemist. While mild conditions exist for the reduction of simple ketones and aldehydes, the reduction of esters has typically required more powerful hydride reagents.[4] By far, the most well known reagents to effect this transformation are aluminum hydrides, such as lithium aluminum hydride (LAH) and a variety of alkoxy aluminum hydrides.[5] There are several shortcomings associated with the use of these compounds. Of primary concern is their extreme pyrophoricity. This becomes an almost overwhelming problem when the reaction is run on an industrial scale, and has led to some companies barring the use of LAH entirely. Other problems include the lack of chemoselectivity (LAH also reduces halides, alkynes and epoxides[4]) and the possibility of forming insoluble aluminum-bound salts of the desired products, especially with chelating products such as diols.

The hydrosilylation reaction presents a useful alternative to aluminum hydride mediated carbonyl reductions. As the name implies, the reaction proceeds by the addition of a silicon-hydrogen bond across a unit of unsaturation, usually catalyzed by a transition-metal complex (eq 7). While the transition metal-catalyzed hydrosilylation of



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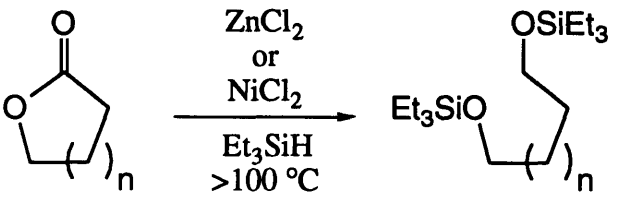
olefins, alkynes, and ketones has been the subject of much study,[6] relatively little is known about the hydrosilylation reaction of esters. All the systems investigated require harsh reaction conditions or a stoichiometric amount of metal reagent. Calas has demonstrated the reduction of lactones by triethylsilane in the presence of $ZnCl_2$ at elevated temperatures.[7] Frainnet has achieved similar results using $NiCl_2$[8] (eq 8).

γ-Irradiation has also been shown to induce the reaction of trichlorosilane with esters to form ethers[9] (eq 9).



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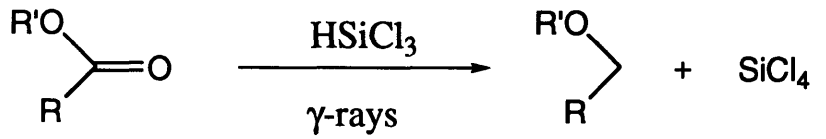
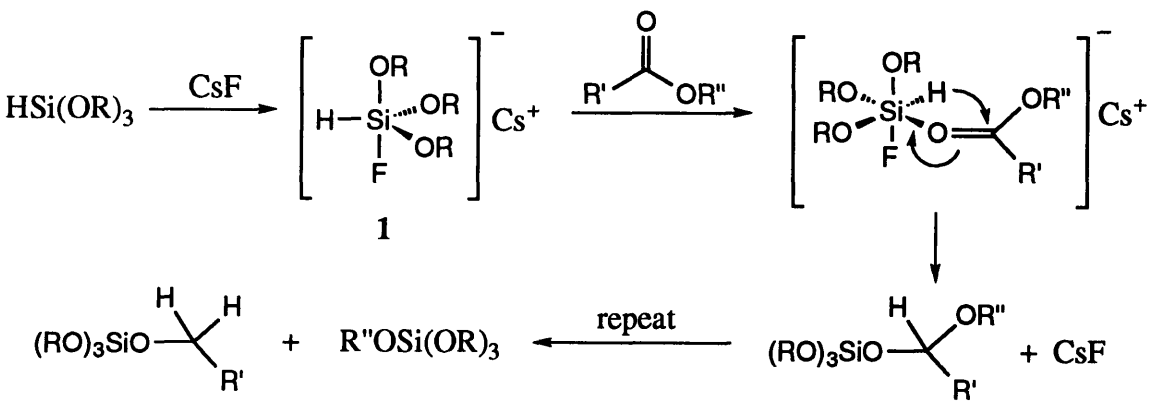
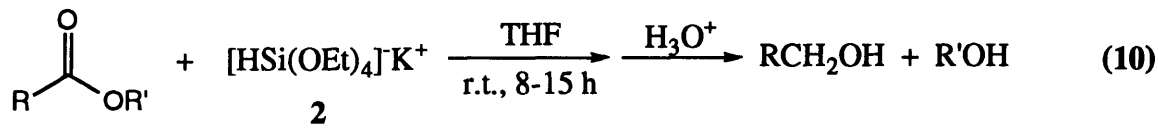


(9)

Corriu and co-workers have developed much milder conditions by activating triethoxysilane with stoichiometric quantities of fluoride salts in the absence of solvent.[10a,b] They were also able to use an inexpensive polymer, polymethylhydrosiloxane, in the place of triethoxysilane as the stoichiometric reductant, but this modification required the use of DMSO as the solvent and heating the reaction mixture to 80 °C.[10a,c] Corriu implicated a pentavalent anionic silicon species **1** as the active reducing agent (Scheme 1). To support this claim, hydridosilicate species **2** was synthesized and shown to rapidly reduce esters in THF at room temperature[49b] (eq 10).

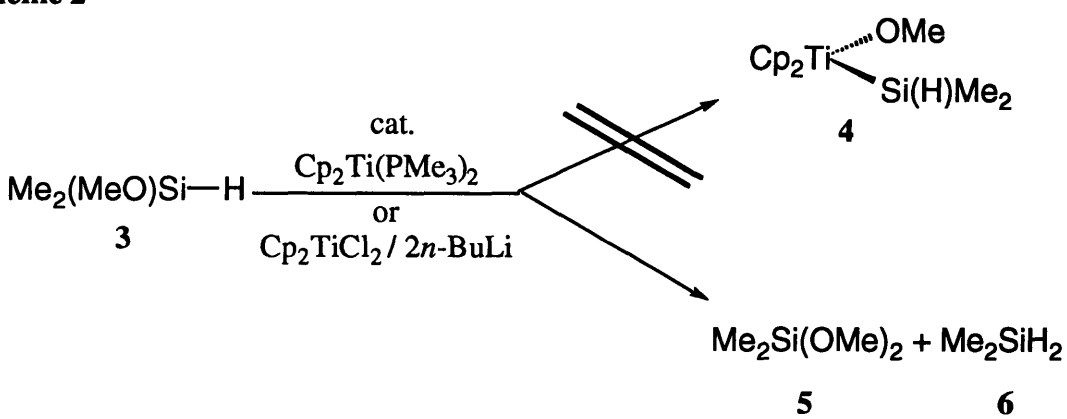
Scheme 1





We became interested in ester reduction as a result of a discovery made by Kristina Kreutzer. As part of a study on the reactive intermediates involved in silane oligomerization processes, she was attempting to synthesize the titanocene silyl hydride complex **4** by the reaction of silane **3** with the phosphine-stabilized titanocene equivalent, $Cp_2Ti(PMe_3)_2$ (Scheme 2).[11] Instead of the desired product she observed only the silane redistribution products **5** and **6**.[12] She also noticed $Cp_2Ti(PMe_3)_2$ present in the product mixture, which led her to try the redistribution reaction using only a catalytic amount of $Cp_2Ti(PMe_3)_2$. She found that under these conditions, the reaction still went to completion rapidly at room temperature. Kreutzer also found that an active catalyst system could be conveniently generated *in situ* by the reaction of 2 equiv of *n*-BuLi with Cp_2TiCl_2,[11b,13] an inexpensive, air-stable and commercially available solid. Since $Cp_2Ti(PMe_3)_2$ is very air-sensitive and must be stored and handled in a dry box, this practical modification allowed the reaction to be run using standard air-free organic laboratory techniques.

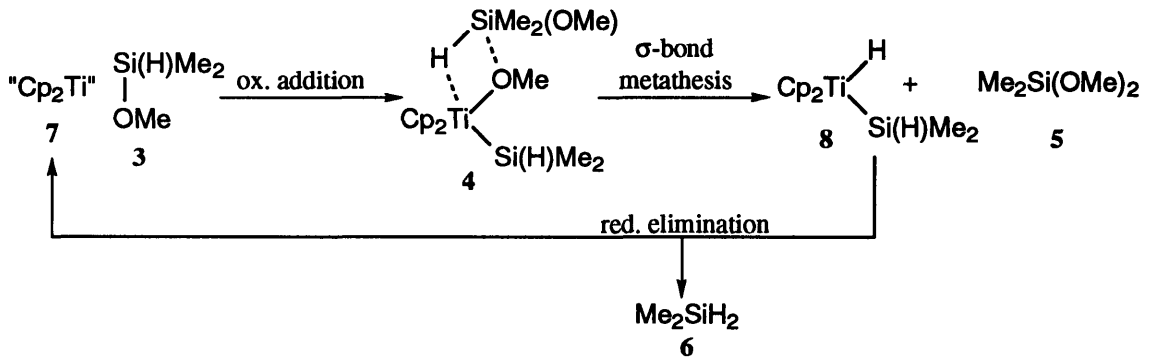
Scheme 2



While a titanium-catalyzed conversion of an expensive, complex starting material into two inexpensive, simple products had little practical value, Kreutzer realized that the

reaction proceeded through a potentially novel mechanism (Scheme 3). The proposed catalytic cycle begins with oxidative addition of the silicon-oxygen bond of **3** to reactive "titanocene" **7** to afford titanocene silyl alkoxide **4**. Reaction of this d^0 complex with another molecule of **3** may then proceed through a four-centered, σ-bond metathesis reaction[14] to afford product **5** and titanocene silyl hydride **845**. A reductive elimination reaction of this intermediate produces the second silane product, **6** and regenerates the active titanocene catalyst.

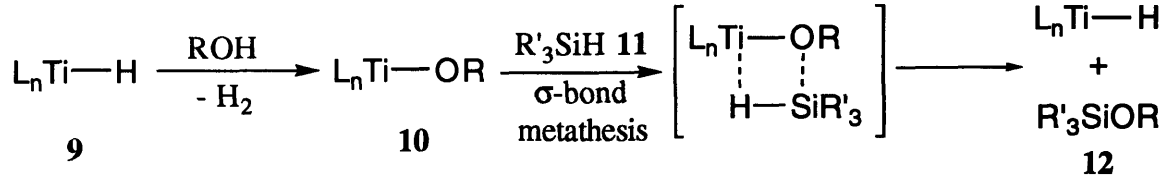
Scheme 3



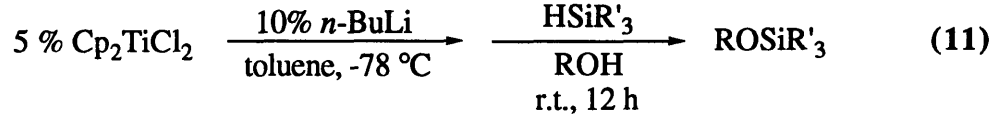
An intriguing aspect of this mechanism was that it involved the making and breaking of strong titanium-oxygen[15] and silicon-oxygen[16] bonds (106 kcal/mol and 115 kcal/mol, respectively) rapidly at room temperature. Pivotal to the success of the reaction is the easy interconversion between a Ti-O bond and a Ti-H bond. With this in mind, we began to envision other more useful organic transformations which could potentially exploit this cycle. It had been demonstrated that early transition metal hydrides were more hydridic than protic in nature.[17] One potential reaction of such a metal hydride **9** is protonation by an alcohol[18] to produce H_2 and the corresponding metal alkoxide **10** (Scheme 4). Based on Kreutzer's proposed mechanism, we envisioned a catalytic cycle where the alkoxide **10** could further react with a silane **11** via a σ-bond metathesis reaction to produce the silyl ether **12** and to regenerate the active hydride catalyst. Kreutzer and Benjamin Warner demonstrated the viability of such a process. They found

that the combination of 5 mol % of Cp_2TiCl_2 and 2 equiv (per catalyst) of *n*-BuLi led to an active catalyst system which cleanly converted a variety of alcohols and silanes into the corresponding silyl ethers with concomitant evolution of H_2[19] (eq 11).

Scheme 4



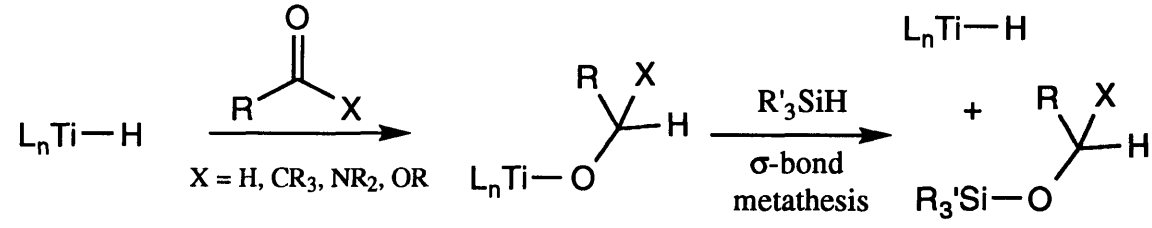
9 10 12



(11)

Encouraged by these results, we decided to explore another possible reaction of early transition metal hydrides **9**, the reduction of carbonyl compounds.[18] We imagined a catalytic cycle where initial 1,2-insertion of the carbonyl compound into the Ti-H bond of **9** would produce alkoxide **13** (Scheme 5). This intermediate could again undergo a σ-bond metathesis reaction, regenerating the catalyst and producing silyl ether **14**, the formal reduction product of the carbonyl compound. When initial NMR tube experiments demonstrated the feasibility of this process, we devoted our efforts to developing a mild, efficient, titanium-catalyzed[20] ester reduction procedure which would hopefully offer an alternative to classical ester reduction reagents,[5] especially for large scale reactions.

Scheme 5

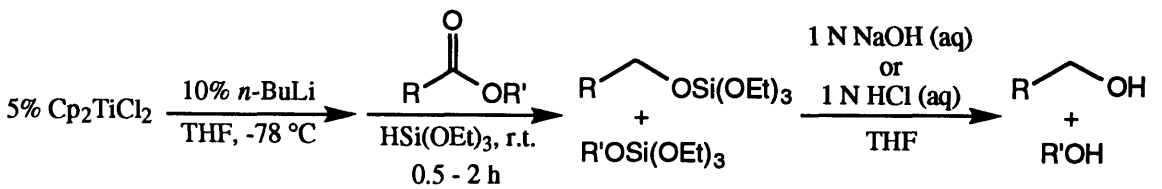


9 **13** **14**

Results and Discussion

The optimized titanocene-catalyzed ester hydrosilylation reaction is shown in Scheme 6. The active catalyst system is generated by the reaction of 2 equiv (per catalyst) of *n*-BuLi with Cp_2TiCl_2 in THF at -78 °C. Addition of 2.5 equiv (per substrate) of silane and the ester to be reduced, followed by warming to room temperature, results in an exothermic reaction which cleanly produces the corresponding silyl ethers. Acid or alkaline hydrolysis then affords the alcohol products in very good yields. The reaction works well using triethoxysilane, diphenylsilane or diethylsilane as the stoichiometric reductant. However, when triethoxysilane[21] is used, the hydrolysis proceeds very cleanly, generally affording crude products of greater than 90% purity, as judged by ^1H NMR and GC analysis. The bulkier phenyldimethylsilane produces no catalytic turnover. We have also found that the catalyst loading can be reduced to 0.5 mol % with no loss of yield. Most of the reduction reactions presented here, however, were run on a 2 mmol scale using 5 mol % of catalyst.

Scheme 6



The reaction works well for a large variety of ester substrates (see Table 1). Simple aromatic, heteroaromatic and aliphatic esters (Table 1, entries 1-5, 12 and 13) are reduced in very high yield under the standard reaction conditions. Scale-up of the reaction was also not problematic. Methyl benzoate (Table 1, entry 1) was reduced on a 100 mmol scale to afford benzyl alcohol in 93% yield after acid hydrolysis of the intermediate silyl ether. Di- and tri-substituted olefins, including a tri-substituted α,β-unsaturated ester, are completely tolerated during the reaction (Table 1, entries 6-8).

Certain functional groups require some modification of the reaction conditions to allow for complete conversion. Running the reaction in the presence of esters containing

terminal olefins leads to catalyst deactivation, probably through an irreversible insertion reaction of the olefin into a Ti-H bond.[22] We have found that by replacing the pre-catalyst, Cp_2TiCl_2, with the sterically more hindered titanocene complex, ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride,[23] (EBTHI)$TiCl_2$, the approach of the terminal olefin is sufficiently restricted to allow the ester reduction reaction to proceed to completion (Table 1, entry 9). Under standard conditions, the reaction of a bromo ester fails to go to completion due to a stoichiometric titanium-mediated dehalogenation reaction.[24] This unwanted side reaction can be attenuated by running the reaction at -20 °C, followed by slow warming to room temperature (Table 1, entry 10). An ester containing a terminal epoxide was also not tolerated under the standard reaction conditions. The catalyst was deactivated before reduction was complete, and epoxide deoxygenation products could be identified in the crude reaction mixture. It has been shown that epoxides are deoxygenated and reduced by titanocene[25] and titanium (III) complexes.[26] We have found that the rate of catalyst deactivation can be decreased in this instance by the use of the sterically hindered (EBTHI)$TiCl_2$ pre-catalyst (Table 1, entry 11). Extra equivalents of silane are required for esters containing acidic protons (Table 1, entries 14 and 15), since these functional groups are silylated under the reaction conditions. For example, when methyl 4-hydroxybenzoate (Table 1, entry 14) is reduced in the presence of 3.5 equiv of triethoxysilane, the reaction first silylates the phenol. During this phase of the reaction, bubbles of H_2 are evolved. When the silylation phase is complete, gas evolution ceases and the reduction reaction begins.

Selective reduction of an ester in the presence of a ketone was not possible. The reaction of ethyl 4-acetylbutyrate (Table 1, entry 16) using 2.5 equiv of silane provided a low yield of the fully-reduced diol along with some ketone-reduced product. Complete conversion of the keto-ester could be effected by the use of 3.3 equiv of silane. A methyl ester can be selectively reduced in the presence of a *t*-butyl ester (Table 1, entry 17).[27] In fact, *t*-butyl esters are completely inert under the reaction conditions.

Table 1. Titanocene-Catalyzed Reduction of Esters

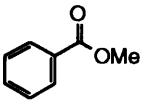
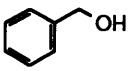
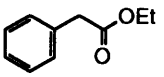
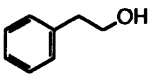
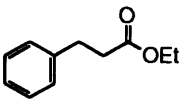
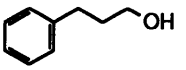
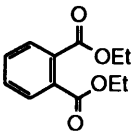
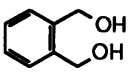
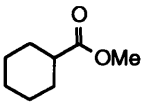
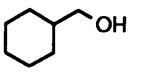
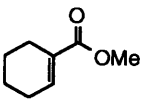
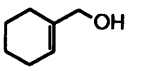
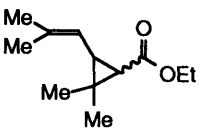
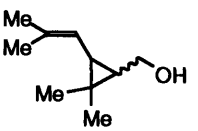
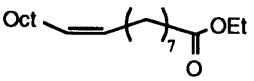
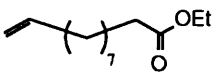
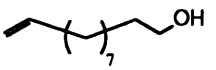
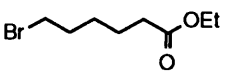
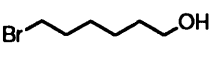
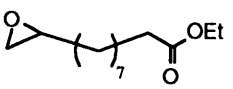
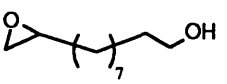
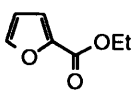
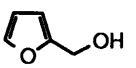
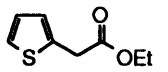
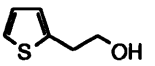
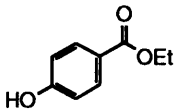
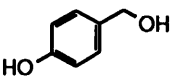
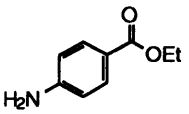
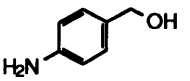
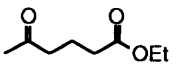
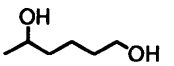
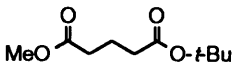
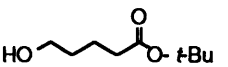
Entry	Ester	Procedure[a]	Workup	Product	Yield (%)
1		A	conc. HCl		93[b]
2		A	1 N NaOH in MeOH		81
3		A[c]	1 N NaOH in MeOH		82
4		A	1 N NaOH in H_2O extract with EtOAc		81
5		A	conc. HCl		85
6		A	1 N NaOH in H_2O		71
7		A	1 N NaOH in EtOH		83
8		A	1 N NaOH in H_2O		90
9		B[e]	1 N NaOH in H_2O		62
10		B[d]	1 N NaOH in H_2O		78
11		B[e]	1 N NaOH in H_2O		67
12		A	1 N NaOH in H_2O		75

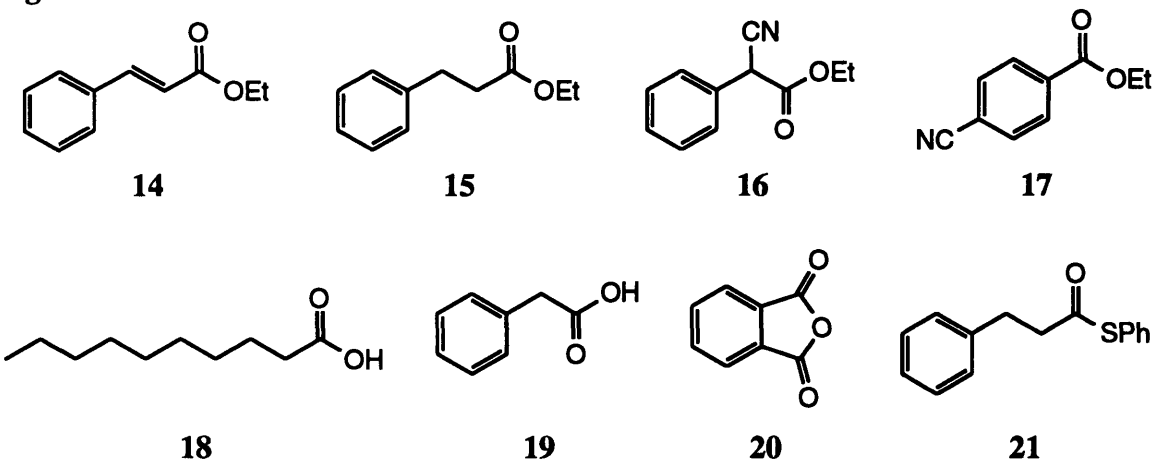
Table 1 (cont.)

Entry	Ester	Procedure[a]	Workup	Product	Yield (%)
13		A	1 N NaOH in H_2O		88
14		A[f]	1 N NaOH in H_2O extract with EtOAc		88
15		A[g]	1 N NaOH in H_2O extract with EtOAc		81
16		A[f]	1 N NaOH in H_2O extract with EtOAc		78
17		A	1 N NaOH in H_2O		87

[a]Procedure A: Silane and ester are added to the precatalyst mixture simultaneously. Procedure B: Silane is added to the pre-catalyst mixture and the reaction mixture is warmed to r.t., during which time gas evolution is observed. The ester is added after gas evolution ceases. See Experimental Section for detailed procedures. [b]100 mmol scale. [c]Ph_2SiH_2 was used in place of $HSi(OEt)_3$. [d]The reaction was run at -20 °C for 6 h, followed by warming to r.t. for an additional 2 h. [e]The reaction was run using (EBTHI)$TiCl_2$ as a pre-catalyst in place of Cp_2TiCl_2. [f]An additional equiv of $HSi(OEt)_3$ (3.3 equiv total) was necessary for complete reaction. [g]An additional 2 equiv of $HSi(OEt)_3$ (4.8 equiv total) was necessary for complete reaction.

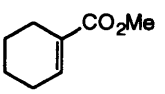
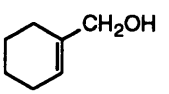
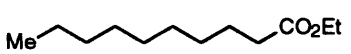
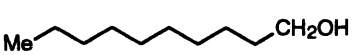
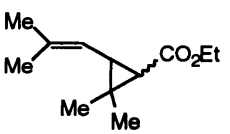
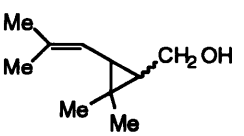
Several substrates were more problematic (see Figure 1). The reaction with the disubstituted α,β-unsaturated ester **14** gave, after work-up, poor yield (10-15%) of the double bond reduction product **15** along with unreacted starting material. Performing the reaction using (EBTHI)$TiCl_2$ as the pre-catalyst resulted in no improvement. The reduction of cyano esters **16** and **17** did not turn over catalytically, presumably due to the known stoichiometric nitrile reduction reaction,[28] which would deactivate the catalyst. Carboxylic acids **18** and **19**, anhydride **20**, and thiolester **21** also did not react, affording only starting material after work-up.

Figure 1



We have found that we can use the inexpensive siloxane polymer, polymethylhydrosiloxane (PMHS),[29] as an effective substitute for triethoxysilane as the stoichiometric reducing agent. This became especially important in light of safety concerns associated with the use of simple alkoxysilanes.[21] Table 2 lists several substrates which were reduced using PMHS as the stoichiometric reductant. For most cases,[30] yields are comparable to those obtained using triethoxysilane. We have also found that non-pyrophoric EtMgBr can be used in place of *n*-BuLi to generate an active catalyst system. These simple modifications should render this reaction more synthetically useful, especially for large scale applications.

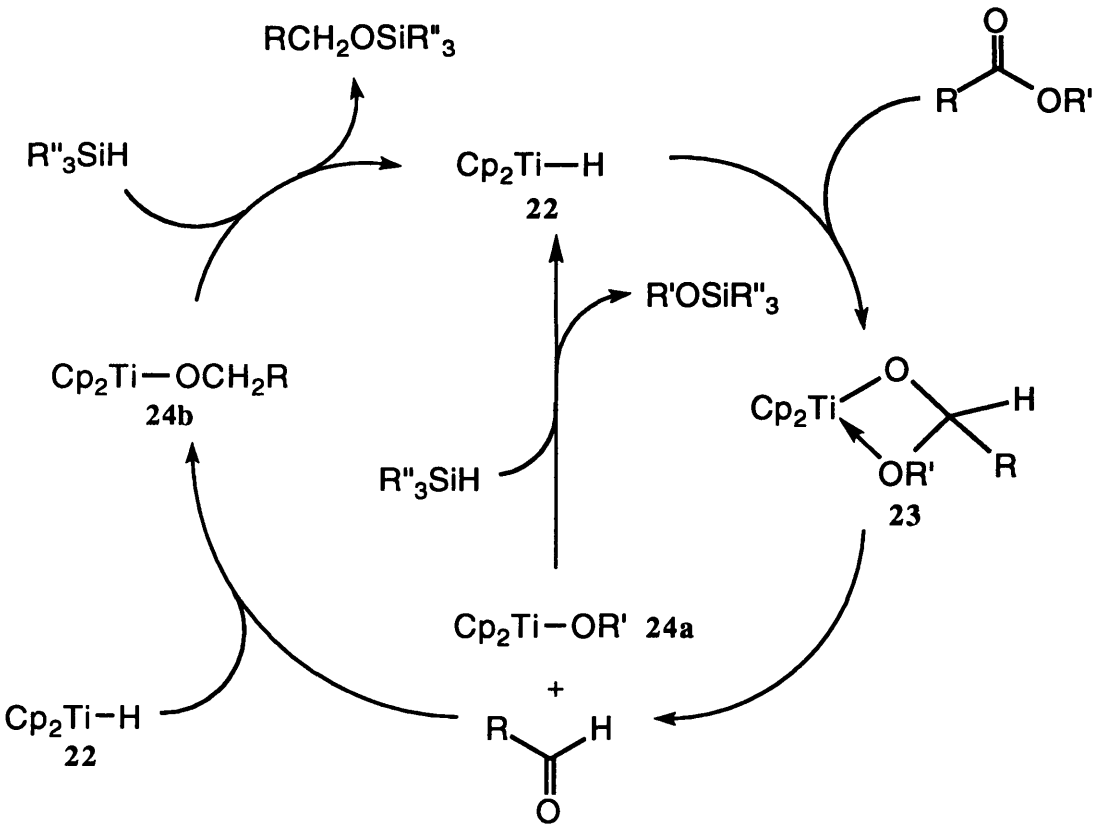
Table 2. Titanocene-Catalyzed Reduction of Esters Using Polymethylhydrosiloxane

Entry	Ester	Product	Yield (%)[a]
1			63 (71)
2			98
3			90 (88)

[a]Numbers in parentheses refer to yield obtained using $HSi(OEt)_3$.

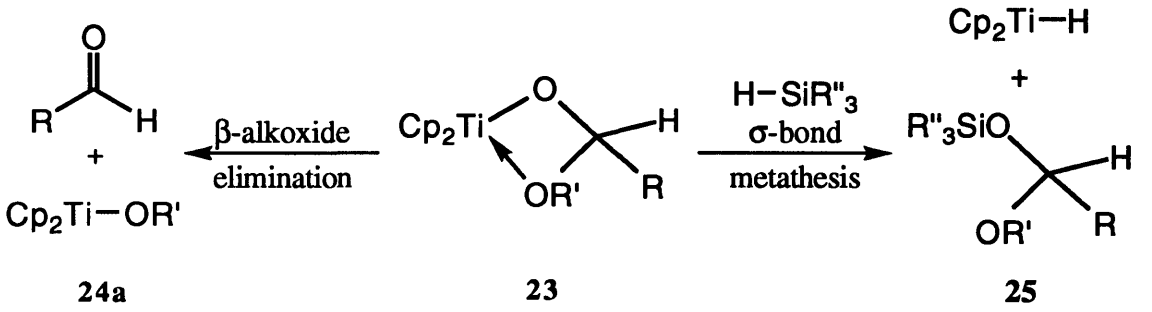
While we have not yet undertaken detailed mechanistic studies, a plausible catalytic cycle for the reaction is outlined in Scheme 7. We believe that the active catalyst in this system is a titanium (III) complex. There are several reasons for this hypothesis: The +3 oxidation state is very accessible to titanium, and the propensity of titanium (IV) to be reduced is known.[31] We also observe complete disappearance of ^{1}H NMR signals attributable to the titanium species under the conditions of the reaction. This is expected for a paramagnetic titanium (III) complex. We also note that several side reactions which we have observed with epoxides and olefins have been attributed to titanium (III) reagents.[22,26] Finally, titanium (III) has been implicated as the reactive intermediate in transformations which begin with the addition of two or more equiv of alkyllithium or alkyl Grignard reagents to Cp_2TiCl_2.[22,32] Thus, our proposed mechanism begins with bis(cyclopentadienyl)titanium (III) hydride complex **22**, probably generated through a one electron reduction of the dichloride by the alkyllithium, followed by formation of a titanocene (III) alkyl species.[22] β-Hydride elimination can then afford **22**. Initial interaction of the ester substrate with **22** leads to a 1,2-insertion reaction into the Ti-H bond to give titanocene alkoxide **23**, in which the second ester oxygen atom is datively coordinated to the titanium atom. This interaction may then lead to a β-alkoxide elimination reaction, expelling aldehyde to produce titanocene alkoxide **24a**. The aldehyde is never observed in the reaction mixture. It is immediately reduced by another equivalent of **22**, giving rise to the insertion product **24b**. Both titanium alkoxides, **24** can then undergo σ-bond metathesis reactions[14] with silane to regenerate the active catalyst **22** and afford the product silyl ethers.

Scheme 7



We were especially interested in the existence of proposed intermediate alkoxide **23**. We reasoned that if we could somehow modify the reaction conditions to induce a σ-bond metathesis reaction to occur at this stage, the catalyst would be regenerated along with a silyl protected hemiacetal **25** (Scheme 8). Kreutzer had shown that acetals were inert to the reaction conditions,[12] so this modification would serve as a route to produce an aldehyde in a protected form. Hydrolysis of **25** would then liberate the desired product, providing a simple and useful method to convert esters to aldehydes. The classical way to effect this transformation is through the use of diisobutylaluminum hydride, but this reaction suffers several drawbacks. It must be run at very low temperature (-78 °C), and its success is highly substrate dependent.[33] Thus, we turned our attention to developing the proper reaction conditions which would convert esters to the corresponding silyl-protected hemiacetals, and ultimately, to aldehydes.

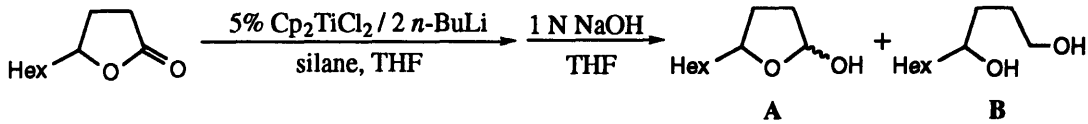
Scheme 8



24a **23** **25**

To make σ-bond metathesis (**23** to **25**) more competitive, we replaced triethoxysilane with phenylsilane, a sterically smaller reagent with more reactive Si-H bonds.[34] We also deemed it necessary to reduce the facility of the β-alkoxide elimination pathway (**23** to **24a**). We hoped to shut down this step by attenuating the titanium to oxygen dative interaction in **23**. In hopes of blocking this coordination, we modified the cyclopentadienyl ligands on the titanium, utilizing the bulkier and more electron-donating pentamethylcyclopentadienyl ligand. We also tried using sterically hindered **R'** groups on the ester (*i*-propyl and *t*-butyl). This is how we discovered that *t*-butyl esters are inert to reduction. To make the coordination less electronically favorable, we attempted to make the ester oxygen less electron rich, replacing **R'** with electron withdrawing groups, such as the trifluoroethyl group. None of these modifications resulted in any observable formation of **25** from simple esters. When the ester substrate had **R** and **R'** tethered together by a carbon chain, as in a lactone, we were able to observe a substantial amount of lactol in the crude product mixture (lactol : diol ratio = 1.8 : 1). Evidently, the tether places a geometric constraint on the dative interaction in intermediate **23**. This constraint may arise from bumping interactions of the carbon tether with the cyclopentadienyl ligands on titanium. With this result in hand, we could then further optimize the reaction conditions to increase the lactol : diol ratio. Table 3 outlines the results of this work. We found that by using the more reactive hydrosilylation reagent, phenylsilane, and running the reaction at 0 °C, we could achieve almost exclusive formation of the lactol after the usual work-up.

Table 3. Optimization of the Titanocene-Catalyzed Reduction of Lactones to Lactols

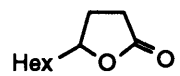
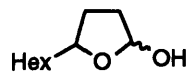
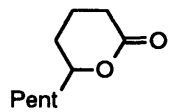
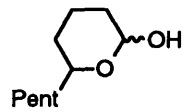
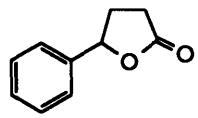
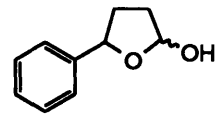
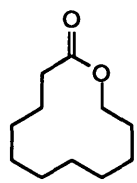
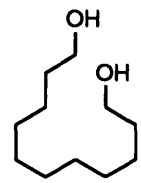


A **B**

Silane	Temperature	Ratio **A** : **B**
$HSi(OEt)_3$	25 °C	1.8 : 1
$HSi(OEt)_3$	0 °C	4.8 : 1
$HSi(OEt)_3$	-20 °C	8.0 : 1
H_3SiPh	25 °C	3.2 : 1
H_3SiPh	0 °C	22 : 1
H_3SiPh	-20 °C	no reaction

These results are in line with our mechanistic predictions (see Scheme 8). The unimolecular β-alkoxide elimination pathway is entropically favored over the bimolecular σ-bond metathesis step. Lowering the temperature of the reaction reduces the favorable entropy contribution associated with the activation energy of the elimination pathway, thus making the σ-bond metathesis pathway more competitive. Table 4 shows the application of these results to the conversion of several lactones to lactols. For five- and six-membered ring lactones, the reaction works quite well, affording the lactol products in 69-94% yield. When the ring size of the lactone is expanded, however (Table 4, entry 4), the geometric constraint on the titanium-oxygen dative interaction is relaxed, and the reaction again proceeds through the β-alkoxide elimination pathway, resulting in exclusive diol formation.[35]

Table 4. Titanocene-Catalyzed Reduction of Lactones to Lactols

Entry	Lactone	Lactol : Diol[a]	Product	Yield (%)[b]
1		22 : 1		83
2		28 : 1		94
3		3 : 1		69
4		0 : 1		88

[a]Based on ^{1}H NMR analysis of the crude product. [b]Yields refer to isolated yields of pure lactols. For entry 4, the exclusive product is the diol.

In conclusion, we have developed a mild, efficient ester reduction protocol which tolerates a wide range of functional groups with little or no modification to the standard reaction conditions. We have also used a mechanism-based approach to develop a modification of the reaction conditions for the conversion of lactones to lactols. In addition, we note that the reaction is experimentally simple, and relatively insensitive to adventitious moisture or air. The reaction proceeds cleanly, even when the substrate is pre-mixed with 10 mol % of H_2O (excess silane is used to scavenge water, which is silylated under the reaction conditions) or if the reaction is carried out in a solvent which has not been rigorously dried and deoxygenated. Moreover, the reaction can be run at high substrate concentrations and low catalyst loading (as low as 0.5 mol %) with no noticeable decrease in yield. Still there was room for improvement, and we again turned to our proposed mechanism to develop a second generation reduction system with even more desirable properties.

Experimental Section for Chapter 1, Part 1

General Considerations

All reactions were conducted under an atmosphere of purified argon using standard Schlenk techniques. Tetrahydrofuran (THF) was dried and deoxygenated by refluxing over sodium/benzophenone ketyl followed by distillation under argon. Cp_2TiCl_2 was purchased from Boulder Scientific Inc., Mead, Colorado. Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanocene dichloride, (EBTHI)$TiCl_2$, was prepared according to the published procedure.[37] Methyl 10,11-epoxyundecanoate was prepared by *m*-CPBA oxidation of methyl 10-undecenoate.[38] *t*-Butyl 4-(carbomethoxy)butyrate was prepared by dropwise addition of commercially available methyl 4-(chloroformyl)butyrate to a refluxing solution of *t*-butanol, dimethylaniline, and 10 mol % of DMAP in ether. All other reagents were available from commercial sources and were purified before use by passage through a short column of neutral alumina (ICN Alumina N, Akt I).

Preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230-400 mesh). All products, unless otherwise noted, are commercially available.[36] Yields, unless otherwise noted, refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and/or ^1H NMR analysis. All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian Unity 300, or a Bruker AC-250 Fourier transform spectrometer. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; 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 the central line of the 77.0 ppm triplet for deuterochloroform. Infrared (IR) spectra were recorded on a Mattson Cygnus Starlab 100 or a Perkin-Elmer 1600 Series Fourier transform spectrometer. Gas chromatography (GC) analyses were performed on a Hewlett Packard model 5890 Gas Chromatograph with a 3392A integrator and FID detector using a 25 m capillary column with crosslinked SE-30 as a

stationary phase. Melting points were measured on a Haake Buchler Melting Point Apparatus and are uncorrected.

Typical Procedures for the Titanocene-Catalyzed Reduction of Esters to Alcohols

Procedure A. To a dry Schlenk tube under argon was added Cp_2TiCl_2 (38 mg, 0.15 mmol, 5 mol %) and 2 mL of THF. The slurry was cooled to -78 °C (dry ice/acetone bath) and *n*-butyllithium (188 μL, 1.6 M in hexane, 0.3 mmol) was added. The color of the reaction mixture changed from red to dark brown. After stirring for 15 min, triethoxysilane (1.4 mL, 7.5 mmol) and the ester (3.0 mmol) were added, and the cold bath was removed. As the reaction mixture warmed, gas evolution was apparent (see caution above) and a significant amount of heat was generated which, in certain cases, was enough to reflux the THF. (**NOTE:** For large scale reactions, it is recommended that a room temperature water bath be used in order to avoid excess heating.) After 0.5 - 2 h, GC analysis of an aliquot taken from the reaction mixture showed complete disappearance of the starting material. The catalyst was deactivated by exposure to air until the color of the solution changed from dark brown to yellow. THF (5 mL) and 1 N NaOH (15 mL) were then added SLOWLY to avoid bubbling over, and the reaction mixture was stirred vigorously for 1-3 h. The mixture was then added to a separatory funnel with 150 mL each of H_2O and ether. The aqueous layer was separated and extracted with 100 mL of ether. The combined organic extracts were then washed with 100 mL each of 1 N HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to afford the crude product.

Procedure B. To a dry Schlenk tube under argon was added Cp_2TiCl_2 (38 mg, 0.15 mmol, 5 mol %) and 2 mL of THF. The slurry was cooled to -78 °C (dry ice/acetone bath) and *n*-butyllithium (188 μL, 1.6 M in hexane, 0.3 mmol) was added. The color of the reaction mixture changed from red to dark brown. After stirring for 15 min,

triethoxysilane (1.4 mL, 7.5 mmol) was added and the reaction mixture was allowed to warm to r.t. During this time, gas evolution was apparent (see caution above). When bubbling ceased, the reaction mixture was again cooled to -78 °C. The ester (3.0 mmol) was added, and the reaction mixture was again allowed to warm to r.t. After 0.5 - 2 h, GC analysis of an aliquot taken from the reaction mixture showed complete disappearance of the starting material, and the reaction was worked up as described above.

CAUTION! Adequate eye protection is required for the handling of triethoxysilane (vapors can cause blindness). Alkoxysilanes are known to disproportionate to form the highly pyrophoric silane gas (SiH_4). In two reactions where the *n*-BuLi/Cp_2TiCl_2 ratio was greater than 3, opening of the reaction vessel to air caused the appearance of a flame, presumably due to SiH_4. A control experiment in which *n*-BuLi was allowed to react with triethoxysilane in the absence of Cp_2TiCl_2 gave similar results.

Benzyl alcohol (Table 1, entry 1). Using methyl benzoate (13.6 g, 100 mmol) as the substrate, procedure A was followed up to the catalyst deactivation step. Then, THF (100 mL) and concentrated HCl (10 mL) were added to the reaction mixture. After stirring for 1 h, the mixture was added to a separatory funnel with 500 mL each of brine and ether. The aqueous layer was extracted with 2x300 mL ether, and the combined organic extracts were dried over $MgSO_4$. The crude product was purified by vacuum distillation (54 °C, 1 mm Hg) to afford 10.0 g (93% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.1-7.3 (m, 5 H), 4.43 (s, 1 H), 3.87 (s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 140.8, 128.2, 127.2, 126.8, 64.5; IR (neat): 3320, 3088, 3064, 3031, 2931, 2873, 1496, 1453, 1208, 1023, 1019, 735, 698 cm^{-1}.

2-Phenyl-1-ethanol (Table 1, entry 2). Using ethyl 2-phenylethanoate (500 μL, 3.0 mmol) as the substrate, procedure A was followed up to the catalyst deactivation step.

Then, THF (5 mL), methanol (15 mL), and NaOH (0.6 g, 15 mmol) were added to the reaction mixture. After stirring for 2 h, the mixture was worked up as described above. The crude product was purified by flash chromatography (ether : hexane = 1 : 1) to afford 300 mg (82% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.0-7.3 (5 H), 3.68 (t, J = 6.8 Hz, 2 H), 3.29 (s, 1 H), 2.74 (t, J = 6.8 Hz 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.4, 128.7, 128.1, 126.0, 63.1, 38.8; IR (neat): 3086, 3063, 3028, 2942, 2876, 1497, 1453, 1046, 1024, 747, 699 cm^{-1}.

3-Phenyl-1-propanol (Table 1, entry 3). Using ethyl 3-phenylpropionate (712 mg, 4.0 mmol) as the substrate and diphenylsilane (930 μL, 5.0 mmol) in the place of $HSi(OEt)_3$, procedure A was followed up to the catalyst deactivation step. Then, THF (5 mL), methanol (15 mL), and NaOH (0.6 g, 15 mmol) were added to the reaction mixture. After stirring for 2 h, the mixture was worked up as described above. The crude product was purified by flash chromatography (ether : hexane = 2 : 3) to afford 444 mg (82% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.1-7.2 (m, 5 H), 3.5-3.6 (m, 3 H), 2.62 (t, J = 7 Hz, 2 H), 1.80 (quint, J = 6 Hz, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 141.7, 134.2, 128.1, 125.5, 61.6, 33.8, 31.8; IR (neat): 3330, 3085, 3063, 3028, 2942, 2876, 1497, 1453, 1046, 1024, 747 cm^{-1}.

1,2-Benzenedimethanol (Table 1, entry 4). Using diethyl phthalate (596 μL, 3.0 mmol) as the substrate and adding an additional 2 equiv of triethoxysilane (2.5 mL, 13.5 mmol total), procedure A was followed. After work-up (as described, except that 6x100 mL ethyl acetate was used to extract the product from the aqueous layer), the crude product was purified by flash chromatography (ether : hexane = 4 : 1) to afford 335 mg (81% yield) of light yellow crystals: m. p.: 64-65 °C (lit.[36]: 63-65 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (s, 4 H), 4.52 (d, J = 5.1 Hz, 4 H), 4.28 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 129.4, 128.3, 63.5; IR (nujol): 3228, 1401, 1377 1322, 1241,

1213, 1182, 1111, 1038, 1004, 762 cm^{-1}.

Cyclohexanemethanol (Table 1, entry 5). Using ethyl cyclohexane-1-carboxylate (468 mg, 3.0 mmol) as the substrate, procedure A was followed up to the catalyst deactivation step. Then, THF (10 mL) and concentrated HCl (0.5 mL) were added to the reaction mixture. After stirring for 2 h, the mixture was added to a separatory funnel with 50 mL each of brine and ether. The aqueous layer was extracted with 2x50 mL ether, and the combined organic extracts were dried over $MgSO_4$. The crude product was purified by flash chromatography (ether : hexane = 2 : 3) to afford 274 mg (80% yield) of a clear oil: ^1H NMR (250 MHz, $CDCl_3$): δ 3.38 (d, J = 6.4 Hz, 2 H), 3.05 (s, 1 H), 1.6-1.8 (m, 5 H), 1.35-1.55 (m, 1 H), 1.05-1.35 (m, 3 H), 0.8-1.0 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 68.2, 40.2, 29.5, 26.4, 25.7; IR (nujol): 3330, 2918, 2853, 2796, 1472, 1462, 1449, 1430, 1419, 1378, 1100, 1091, 1080, 1056, 1034, 1025, 892 cm^{-1}.

Cyclohex-1-ene-1-methanol (Table 1, entry 6). Procedure A was followed to reduce methyl cyclohex-1-ene-1-carboxylate (408 μL, 3.0 mmol). After work-up (as described), the crude product was purified by flash chromatography (ether : hexane = 3 : 7) to afford 239 mg (71% yield) of a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$): δ 5.6 (m, 1 H), 3.94 (s, 2 H), 2.51 (s, 1 H), 1.9-2.1 (m, 4 H), 1.5-1.7 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.4, 122.5, 67.1, 25.4, 24.8, 22.4, 22.3; IR (neat): 3310, 2930, 2891, 2874, 2858, 1447, 1437, 1052, 1007, 773 cm^{-1}.

Chysanthemumyl alcohol (Table 1, entry 7). Using ethyl chrysanthemumate (mixture of *cis* and *trans* isomers) (650 μL, 3.0 mmol) as the substrate, procedure A was followed up to the catalyst deactivation step. Then, THF (5 mL), ethanol (10 mL), and NaOH (0.4 g, 10 mmol) were added to the reaction mixture. After stirring for 2 h, the mixture was worked up as described above. The crude product was purified by flash chromatography

(ether : hexane = 1 : 1) to afford 368 mg (83% yield) of a pale yellow oil, which was a mixture of *cis* and *trans* isomers in a ratio identical to that of the starting material: ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.93-4.98 (m, 1 H, *trans* isomer), 4.85-4.9 (m, 1 H, *cis* isomer), 3.45-3.75 (m, 2 H), 2.66 (s, 1 H), 1.69 (m, 6 H), 1.36 (m, 1 H, *cis* isomer), 1.0-1.2 (m, 7 H), 0.75-0.85 (m, 1 H, *trans* isomer); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 134.7, 132.7, 123.5, 119.0, 63.0, 60.0 34.9, 30.7, 28.6, 28.5, 26.0, 25.5, 25.3, 22.5, 22.0, 21.1, 20.4, 18.2, 18.0, 15.2; IR (neat): 3330, 2967, 2939, 2923, 2875, 1450, 1420, 1122, 1023, 990 cm^{-1}.

9-Octadecen-1-ol (Table 1, entry 8). Procedure A was followed to reduce ethyl oleate (1.1 mL, 3.0 mmol). After work-up (as described), the crude product was purified by flash chromatography (ethyl acetate : hexane = 3 : 7) to afford 725 mg (90% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.35-5.4 (m, 2 H), 3.60 (t, J = 6 Hz, 2 H), 2.26 (s, 1 H), 1.9-2.0 (m, 4 H), 1.5-1.6 (m, 2 H), 1.1-1.3 (m, 22 H), 0.88 (t, J = 6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 130.3, 130.2, 62.8, 32.7, 31.9, 29.6 (two overlapping signals), 29.5 (two overlapping signals), 29.4 (two overlapping signals), 29.3 (two overlapping signals), 29.1, 27.2, 25.7, 22.6, 14.0; IR (neat): 3320, 2953, 2923, 2855, 1466, 1457, 1378, 1057, 966, 722 cm^{-1}.

10-Undecen-1-ol (Table 1, entry 9). Using ethyl 10-undecenoate (396 mg, 2.0 mmol, 5 mol %) as the substrate, procedure B was followed, replacing the Cp_2TiCl_2 pre-catalyst with (EBTHI)$TiCl_2$ (38 mg, 0.1 mmol). After work-up (as described), the crude product was purified by flash chromatography (ether : hexane = 3 : 7) to afford 210 mg (62% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.81 (m, 1 H), 4.9-5.0 (m, 2 H), 3.60 (t, J = 6.5 Hz, 2 H), 2.43 (s, 1 H), 2.0-2.1 (m, 2 H), 1.1-1.6 (m, 14 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 139.1, 114.0, 62.7, 33.7, 32.7, 29.5, 29.4 (two overlapping signals), 29.0, 28.8, 25.7; IR (neat): 3320, 3077, 2925, 2854, 1641, 1465, 1457, 1070, 992, 909

cm^{-1}.

6-Bromohexanol (Table 1, entry 10). Using ethyl 6-bromohexanoate (534 μL, 3.0 mmol) as the substrate, procedure B was followed, holding the temperature of the reaction mixture after ester addition at -20 °C for 6 h before warming to r.t. for an additional 2 h. After work-up (as described), the crude product was purified by flash chromatography (ether : hexane = 1 : 1) to afford 423 mg (78% yield) of a clear oil: ^1H NMR (250 MHz, $CDCl_3$): δ 3.60 (t, J = 6.5 Hz, 2 H), 3.42 (t, J = 7 Hz, 2 H), 2.99 (s, 1 H), 1.87 (quint, J = 7 Hz, 2 H), 1.3-1.6 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 62.2, 33.7, 32.5, 32.2, 27.7, 24.8; IR (neat): 3330, 2934, 2887, 2859, 1460, 1437, 1430, 1259, 1072, 1053, 1037 cm^{-1}.

10,11-Epoxyundecan-1-ol (Table 1, entry 11).[39] Using methyl 10,11-epoxy-1-undecanoate (428 mg, 2.0 mmol) as the substrate, procedure B was followed, replacing the Cp_2TiCl_2 pre-catalyst with (EBTHI)$TiCl_2$ (38 mg, 0.1 mmol, 5 mol %). After work-up (as described), the crude product was purified by flash chromatography (ether : hexane = 2 : 3) to afford 250 mg (67% yield) of a clear oil: ^1H NMR (250 MHz, $CDCl_3$): δ 3.60 (t, J = 6.5 Hz, 2 H), 2.91 (m, 1 H), 2.75 (m, 1 H), 2.45-2.50 (m, 2 H), 1.2-1.6 (m, 16 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 62.6, 52.3, 46.9, 32.6, 32.3, 29.2 (4 overlapping signals), 25.7, 25.6; IR (neat): 3400, 2927, 2856, 1465, 1410, 1071, 1056, 835 cm^{-1}.

Furfuryl alcohol (Table 1, entry 12). Procedure A was followed to reduce ethyl furoate (420 mg, 3.0 mmol). After work-up (as described), the crude product was purified by Kügel-Rohr distillation under aspirator pressure (b.p. ≈ 80 °C) to afford 220 mg (75% yield) of a yellow oil: ^1H NMR (250 MHz, $CDCl_3$): δ 5.54 (d, J = 2 Hz, 1 H), 4.49 (dd, J_1 = 2 Hz, J_2 = 3 Hz, 1 H), 4.42 (d, J = 3 Hz, 1 H), 2.68 (s, 2 H), 1.88 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 154.0, 142.2, 110.1, 107.4, 56.7; IR (neat): 3340, 3169, 3153,

2930, 2876, 1505, 1221, 1149, 1009, 913, 885, 744 cm^{-1}.

2-(2-Thienyl)ethanol (Table 1, entry 13). Procedure A was followed to reduce ethyl 2-thiopheneacetate (450 μL, 3.0 mmol). After work-up (as described), the crude product was purified by flash chromatography (ethyl acetate : hexane = 3 : 7) to afford 339 mg (88% yield) of a yellow oil: ^1H NMR (250 MHz, $CDCl_3$): δ 7.12 (dd, J_1 = 5 Hz, J_2 = 1 Hz, 1 H), 6.92 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1 H), 6.83 (dd, J_1 = 2 Hz, J_2 = 1 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 140.7, 126.8, 125.3, 123.7, 63.1, 33.0; IR (neat): 3320, 3106, 3070, 2942, 2928, 2878, 1439, 1427, 1077, 1044, 847, 823, 697 cm^{-1}.

4-Hydroxybenzyl alcohol (Table 1, entry 14). Using ethyl 4-hydroxybenzoate (500 mg, 3.0 mmol) as the substrate and adding an additional one equiv of triethoxysilane (1.85 mL, 10 mmol total), procedure A was followed. After work-up (as described, except that 6x100 mL ethyl acetate was used to extract the product from the aqueous layer), the crude product was recrystallized from ether/ethyl acetate to afford 326 mg (88% yield) of light yellow crystals: m. p.: 113-115 °C (lit.:[36] 118-122 °C); ^1H NMR (250 MHz, acetone-d_6): δ 8.28 (s, 1 H), 7.17 (d, 2 H, J = 6 Hz), 6.77 (d, 2 H, J = 6 Hz), 4.50 (d, 2 H, J = 6 Hz), 4.17 (t, 1 H, J = 6 Hz); ^{13}C NMR (62.5 MHz, acetone-d_6): δ 157.3, 134.0, 129.1, 115.7, 64.5; IR (KBr): 3400, 3100, 1612, 1598, 1507, 1456, 1223, 1209, 995, 838 cm^{-1}.

4-Aminobenzyl alcohol (Table 1, entry 15). Using ethyl 4-aminobenzoate (496 mg, 3.0 mmol) as the substrate and adding an additional two equiv of triethoxysilane (2.7 mL, 15 mmol total), procedure A was followed. After work-up (as described, except that 6x100mL ethyl acetate was used to extract the product from the aqueous layer), the crude product was recrystallized from ether/hexane to afford 298 mg (81% yield) of light yellow crystals: m. p.: 62-63 °C (lit.:[36] 65-67 °C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.03

(d, J = 8 Hz, 2 H), 6.60 (d, J = 8 Hz, 2 H), 4.51 (s, 2 H), 4.43 (s, 2 H), 3.92 (s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 146.6, 129.8, 127.3, 113.4, 68.3; IR (KBr): 3350, 3220, 3062, 3028, 2910, 2875, 1620, 1518, 1278, 1183, 1001, 829 cm^{-1}.

1,5-Hexanediol (Table 1, entry 16). Using ethyl 4-acetylbutyrate (480 μL, 3.0 mmol) as the substrate and adding an additional one equiv of triethoxysilane (1.85 mL, 10 mmol total), procedure A was followed. After work-up (as described, except that 6x100 mL ethyl acetate was used to extract the product from the aqueous layer), the crude product was purified by flash chromatography (ethyl acetate) to afford 306 mg (78% yield) of a clear oil: ^1H NMR (250 MHz, $CDCl_3$): δ 4.02 (m, 1 H), 3.74 (m, 2 H), 3.59 (t, J = 6 Hz, 2 H), 1.5-1.4 (m, 6 H), 1.16 (d, J = 6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 67.9, 62.4, 41.8, 39.0, 32.6, 22.2; IR (neat): 3300, 2981, 2932, 2858, 1458, 1432, 1419, 1374, 1133, 1111, 1072, 1050, 945, 923, 733 cm^{-1}.

***t*-Butyl 5-hydroxypentanoate (Table 1, entry 17).**[40] Procedure A was followed to reduce *t*-butyl 4-(carbomethoxy)butyrate (625 μL, 3.0 mmol). After work-up (as described), an ethereal solution of the crude product was decolorized by passing through a column of activated charcoal to afford 455 mg (87% yield) of a clear oil: ^1H NMR (250 MHz, $CDCl_3$): δ 3.63 (t, J = 6 Hz, 2 H), 2.45 (s, 1 H), 2.26 (t, J = 7 Hz, 2 H), 1.5-1.8 (m, 4 H), 1.45 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.2, 80.1, 61.9, 35.0, 31.9, 27.9, 21.1; IR (neat): 3400, 2977, 2935, 2872, 1727, 1457, 1392, 1367, 1252, 1155, 1066 cm^{-1}.

Typical Procedure for the Titanocene-Catalyzed Reduction of Lactones to Lactols

To a dry Schlenk tube under argon was added Cp_2TiCl_2 (38 mg, 0.15 mmol, 5 mol %) and THF (2 mL). The slurry was cooled to -78 °C (dry ice/acetone bath) and *n*-butyllithium (188 μL, 1.6 M in hexane, 0.3 mmol) was added. The color of the reaction mixture changed from red to dark brown. After stirring for 15 min, phenylsilane (494 μL,

4.0 mmol) and the lactone (3.0 mmol) were added, and the reaction mixture was warmed to 0 °C (ice bath). After 1 h, GC analysis of an aliquot taken from the reaction mixture showed complete disappearance of the starting material. The catalyst was then deactivated by exposure to air at 0 °C and stirred until the color of the solution became yellow. The reaction was then worked up as in Procedure A above to afford the crude product.

2-Hydroxy-5-hexyltetrahydrofuran (Table 3, entry 1).[41] The general procedure was followed to reduce γ-decanolactone (539 μL, 3.0 mmol). ^{1}H NMR analysis of the crude product showed a 22 : 1 ratio of lactol : diol. Purification by flash chromatography (ether : hexane = 2 : 3) afforded 424 mg (82% yield) of a clear oil, as a mixture of diastereomers, D1 and D2: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.5-5.6 (m, 1 H, D1), 5.4-5.5 (m, 1 H, D2), 4.4-4.5 (m, 1 H, D1), 4.3-4.4 (m, 1 H, D2), 4.1-4.2 (m, 1 H, D1), 3.9-4.0 (m, 1 H, D2), 1.6-2.2 (m, 4 H, D1 & D2), 1.2-1.6 (m, 10 H, D1 & D2), 0.8-0.9 (m, 3 H, D1 & D2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.3, 98.1, 81.1, 78.4, 37.4, 35.6, 33.9, 32.9, 31.8, 29.5, 29.3, 29.2, 26.2, 26.0, 22.6, 14.0, four signals obscured by others.

2-Hydroxy-6-hexyltetrahydropyran (Table 3, entry 2).[42] The general procedure was followed to reduce δ-decanolactone (539 μL, 3.0 mmol). ^{1}H NMR analysis of the crude product showed a 28 : 1 ratio of lactol : diol. Purification by flash chromatography (ether : hexane = 1 : 1) afforded 449 mg (87% yield) of a clear oil, as a mixture of diastereomers, D1 and D2: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.30 (s, 1 H, D1), 4.71 (m, 1 H, D2), 4.68 (s, 1 H, D2), 4.07 (s, 1 H, D1), 3.95 (m, 1 H, D1), 3.41 (m, 1 H, D2), 1.7-1.9 (m, 2 H), 1.0-1.7 (m, 12 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 96.4, 91.5, 76.4, 68.7, 36.0, 35.7, 32.6, 31.8, 31.7, 30.9, 30.2, 29.8, 25.0, 24.9, 22.5 (two overlapping signals), 22.0, 17.3, 13.9 (two overlapping signals).

2-Hydroxy-5-phenyltetrahydrofuran (Table 3, entry 3).[43] The general procedure was followed to reduce 4-phenylbutyrolactone (539 μL, 3.0 mmol). ^{1}H NMR analysis of the crude product showed a 3 : 1 ratio of lactol : diol. Purification by flash chromatography (ether : hexane = 2 : 3) afforded 339 mg (69% yield) of a clear oil, as a equilibrating mixture of diastereomers, D1 and D2: ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.65-5.75 (m, 1 H, D1), 5.5-5.6 (m, 1 H, D2), 5.2-5.3 (m, 1 H, D1), 4.9-5.0 (m, 1 H, D2), 3.9 (s, 1 H, D2), 4.0 (s, 1 H, D1); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7, 142.3, 128.3 (two overlapping signals), 127.4, 127.3, 126.3, 125.6, 98.8, 98.5, 82.9, 79.6, 34.3, 33.0, 32.8, 32.7.

Undecan-1,11-diol (Table 3, entry 4).[44] The general procedure was followed to reduce ω-undecanolactone (557 μL, 3.0 mmol). The reaction mixture becomes very viscous, perhaps due to polymerization. Additional THF (10 mL) was added to the mixture before work-up (as described above). ^{1}H NMR of the crude product showed only the diol. Purification by recrystallization (ether) afforded 492 mg (88% yield) of a white solid: m. p.: 62-64 °C (lit.:[44] 61 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (q, J = 3.9 Hz, 4 H), 1.57 (quint., J = 7.2 Hz, 4 H), 1.25-1.45 (m, 16 H).

Typical Procedure for the Titanocene-Catalyzed Reduction of Esters Using PMHS as the Stoichiometric Reductant

To a dry Schlenk tube under argon was added Cp_2TiCl_2 (74 mg, 0.3 mmol) and THF (4 mL). The slurry was cooled to -78 °C (dry ice/acetone bath) and *n*-butyllithium (564 μL, 1.65 M in hexanes, 0.6 mmol) was added. After stirring for 15 min, PMHS (570 μL, 9.5 mmol hydride equiv) was added, and the reaction mixture was allowed to warm to r.t. The ester (3.0 mmol) was then added slowly. The reaction became very hot, causing the THF to boil. After 40 min, GC analysis of an aliquot taken from the reaction mixture showed complete disappearance of the starting material. The catalyst was deactivated by exposure to air until the color changed from dark brown to orange. The solution was

transferred to a 100 mL round bottom flask with 10 mL of additional THF. Then, 30 mL of 1 M NaOH was then added SLOWLY (to avoid bubbling over). The mixture bubbled vigorously and was stirred for 1.5 h. The reaction mixture was then added to a separatory funnel with 50 mL each of H_2O and ether. The aqueous layer was separated and extracted with 2x40 mL of ether. The combined organic extracts were washed with 40 mL each of 1 N HCl, sat. aq. $NaHCO_3$, and brine, and then dried over $MgSO_4$ to afford the crude product.

Cyclohex-1-ene-1-methanol (Table 4, entry 1): The general procedure was followed to reduce methyl cyclohex-1-en-1-carboxylate (408 μL, 3.0 mmol). Purification by flash chromatography (ether : hexane = 3 : 7) afforded a pale yellow oil (211 mg, 63% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 5.65-5.7 (m, 1 H), 3.97 (s, 2 H), 1.95-2.1 (m, 4 H), 1.83 (s, 1 H), 1.5-1.7 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 122.9, 67.5, 25.5, 24.9, 22.5, 22.4; IR (neat) 3331, 2998, 2932, 1436, 1269, 1161, 1135, 1052, 1008, 946 cm^{-1}.

Decanol (Table 4, entry 2). The general procedure was followed to reduce ethyl decanoate (696 μL, 3.0 mmol) which afforded, without further purification, 465 mg (98% yield) of a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$): δ 3.62 (t, J = 6.6 Hz, 2 H), 2.01 (s, 1 H), 1.5-1.6 (m, 2 H), 1.2-1.4 (m, 14 H), 0.89 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 62.9, 32.7, 31.9, 29.6, 29.5, 29.4, 29.3, 25.7, 22.6, 14.0; IR (neat) 3330, 2854, 1466, 1378, 1266, 1121, 1058, 843, 721 cm^{-1}.

Chrysanthemumyl alcohol (Table 4, entry 3): The general procedure was followed to reduce ethyl chrysanthemumate (650 μL, 3.0 mmol, mixture of *cis* and *trans* isomers) which afforded, without further purification, 413 mg (90% yield) of the alcohol as a pale yellow oil which was a mixture of *cis* and *trans* isomers in a ratio identical to that of the starting material: ^1H NMR (250 MHz, $CDCl_3$): δ 4.93-4.98 (m, 1 H, one isomer), 4.85-

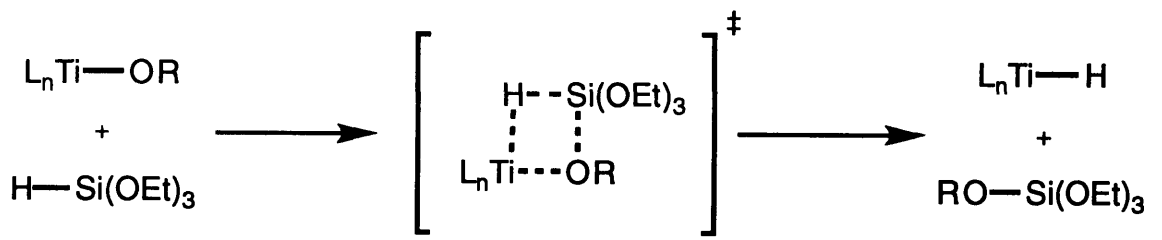
4.90 (m, 1 H, other isomer), 3.45-3.75 (m, 2 H), 1.69 (m, 6 H), 1.36 (m, 2 H), 1.0-1.2 (m, 6 H), 0.75-0.85 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 135.1, 133.1, 123.4, 119.1, 63.6, 60.5, 35.3, 31.2, 28.8, 28.7, 26.3, 25.7, 25.5, 22.7, 22.3, 21.3, 20.7, 18.4, 18.2, 15.5; IR (neat) (cm^{-1}): 3357, 2924, 2877, 1449, 1376, 1122, 1022, 909.

Part 2. The Ti(O-*i*-Pr)$_4$ Reduction System

Introduction

After our initial success with the development of the Cp_2TiCl_2 / 2 *n*-BuLi system, we turned our attention to several shortcomings of the reaction. The biggest drawback of the system was that it was not completely air-stable. Although the reaction still proceeded well in the presence of adventitious moisture and oxygen, opening the reaction vessel to the atmosphere caused rapid catalyst deactivation. The standard reaction conditions also called for air-sensitive metal alkyls, such as *n*-BuLi or EtMgBr to transform the Cp_2TiCl_2 pre-catalyst into the active reduction catalyst. We hoped to find conditions in which the active catalyst could be formed starting with air stable reagents. To achieve this goal, we looked back to our proposed mechanism and noted that the key step in the catalytic cycle is a σ-bond metathesis[14] reaction to convert a titanium alkoxide to a titanium hydride (Scheme 9). We reasoned that an active titanium hydride species might be generated directly from an appropriate titanium alkoxide and the silane used for the reduction, thus eliminating the need for the *n*-BuLi activation step. This expectation was indeed borne out when we found that the combination of a catalytic amount of $Ti(O\text{-}i\text{-}Pr)_4$, and triethoxysilane generates a mild and very efficient ester reduction system.[45]

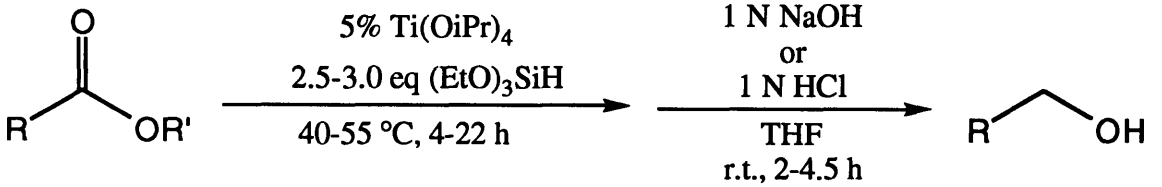
Scheme 9



Results and Discussion

The optimized procedure for the Ti(O-*i*-Pr)$_4$ catalyzed ester reduction reaction is shown in Scheme 10. The reaction is extremely easy to run, and is carried out by simply mixing the ester with 2.5-3.0 equiv of triethoxysilane in a test tube (fitted with a drying tube packed with DrieRite® to exclude excess moisture), adding 5 mol % of Ti(O-*i*-Pr)$_4$, and then heating the reaction mixture to 40-55 °C for 4-22 h. Not only does the use of Ti(O-*i*-Pr)$_4$ lead to a self-activating, air-stable reduction system, but its use imparts other desirable properties onto the reaction. The reaction requires no added solvent, and after acid or alkaline hydrolysis, simple extractive work-up generally provides excellent yields of alcohol products of greater than 95% purity.

Scheme 10



As can be seen from Table 5, the yields from this reaction generally meet or surpass those obtained from the previous system. The reaction also lends itself well to large scale synthesis.[46] Ethyl thiophenacetate (Table 5, entry 2) was reduced on a 50 mmol scale to afford the desired 2-(thienyl)ethanol in 93% yield. The functional group compatibility of this system is also superior to our previous system. Halides and olefins, including terminal olefins, (Table 5, entries 4-6) are completely tolerated under the standard reaction conditions. Epoxides (Table 5, entries 7-9), both terminal and internal, are also unaffected by the reduction process, although some purification of the crude product is necessary to remove traces (less than 5%) of triol which arises from the hydrolysis step. Even a terminal alkyne ester (Table 5, entry 10) was smoothly converted to the desired alkyne alcohol with only traces (~5%) of triple-bond reduction observed. Not surprisingly, free alcohols are silylated under the reaction conditions.[19] Thus, an

alcohol ester (Table 5, entry 11) required an extra equiv of triethoxysilane to afford the desired diol after hydrolysis. A lactone (Table 5, entry 14) was reduced exclusively to the diol with no trace of lactol product detected under a variety of reaction conditions.

While the simple protocol described above works well in many cases, the reduction of some aromatic and cyclopropyl esters stops short of completion. In the cyclopropyl case, this may be due to steric factors. However, since methyl cyclohexane carboxylate (Table 5, entry 12) and methyl 2-phenylbutyrate (Table 5, entry 13) both proceed to completion under the given conditions, the difficulty with reducing benzoate esters cannot be easily explained by steric arguments. The reduction of benzaldehyde is rapid and clean under the standard reduction conditions, so product inhibition of the catalyst is also not responsible for these observations. For these difficult substrates, we have found that complete conversion is achieved by the addition of phenylsilane to the reaction mixture (Table 5, entries 18-20), presumably due to its smaller size and more reactive silicon-hydrogen bonds.[34] Interestingly, reactions of *ortho* substituted benzoate esters (Table 5, entries 15-17) do not suffer from this problem and are reduced to completion in high yield under the standard conditions. This led us to the hypothesis that the reduction of non-*ortho* substituted benzoate esters was getting "stuck" by a C-H activation reaction[47] with the active titanium hydride (Scheme 11) to produce **26**. Intermediate **26**, we reasoned, could be unreactive towards triethoxysilane, but could react with phenylsilane, leading to a species which would turn over catalytically. Unfortunately, running the reduction of methyl benzoate using trideuterophenylsilane provided, after work-up, the alcohol product with no deuterium incorporation in the phenyl ring, casting doubt on the hypothesis. To date, we have not arrived at an adequate explanation for this curious effect. It is an especially surprising result, since benzoate esters are very good substrates for the Cp_2TiCl_2 / 2 *n*-BuLi system, leading us to conclude that the Ti(O-*i*-Pr)$_4$ system potentially proceeds through a very different mechanism.

Table 5. Ti(O-*i*-Pr)$_4$-Catalyzed Reduction of Esters

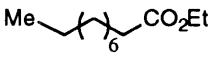
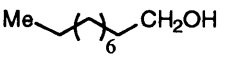
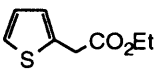
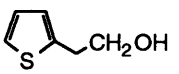
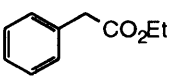
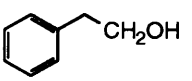
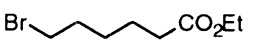
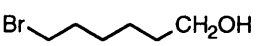
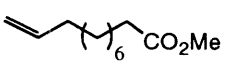
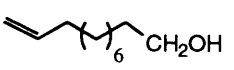
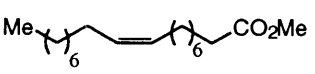
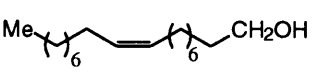
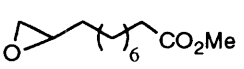
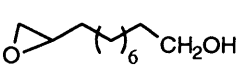
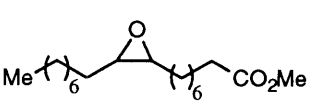
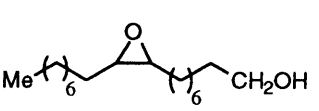
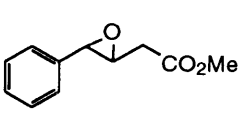
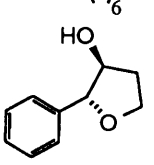
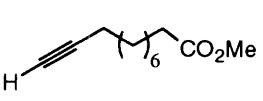
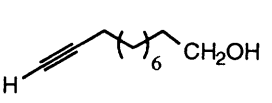
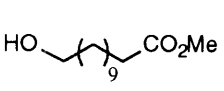
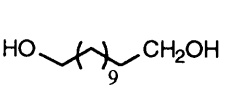
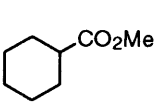
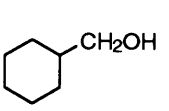
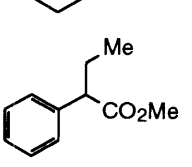
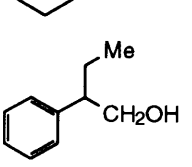
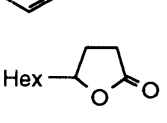
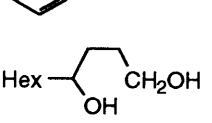
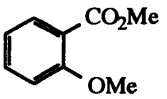
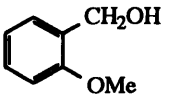
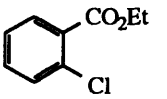
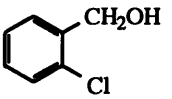
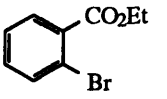
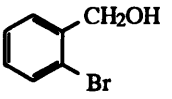
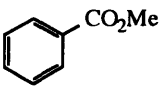
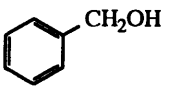
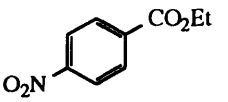
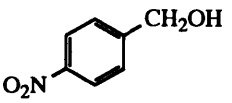
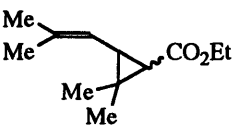
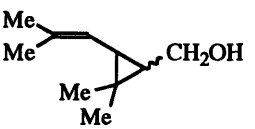
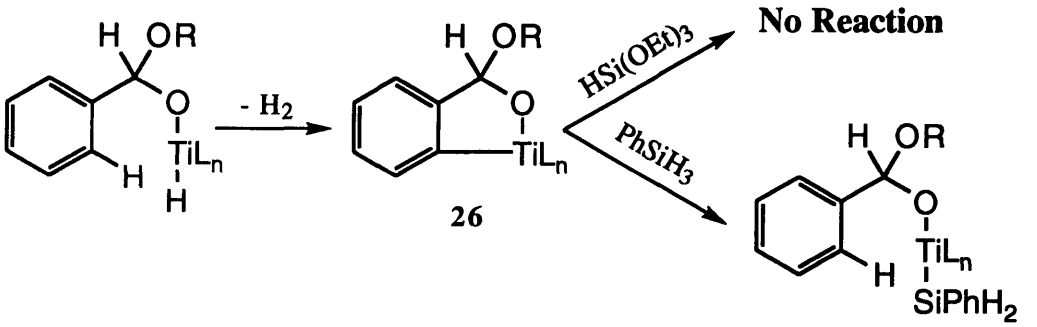
Entry	Ester	Time (h)	Alcohol	Yield (%)
1		10		95
2		4		93[a]
3		4		89
4		6		88
5		16		87
6		5		92
7		21		83[b]
8		18		87[b]
9		5		39
10		18		70[b]
11		7		88[c]
12		16		88
13		14		87
14		16		87

Table 5 (cont.)

Entry	Ester	Time (h)	Alcohol	Yield (%)
15		8		96
16		10		93
17		10		95
18		10		75[d,e]
19		20		75[b,e]
20		22		80[b,e]

[a]50 mmol scale [b]The crude product was purified by flash chromatography or recrystallization. [c]The reaction was run using 3.75 eq of $HSi(OEt)_3$. [d]37 mmol scale, distilled yield [e]Mixtures of $(EtO)_3SiH$ and H_3SiPh are required for complete conversion.

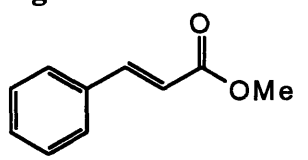
Scheme 11



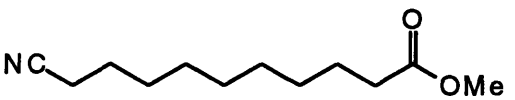
Several other limitations of this method have been discovered (see Figure 2). The reduction of α,β-unsaturated ester **27** proceeded to give a 4 : 1 mixture of 1,2 reduction

and fully saturated products in low (58%) overall yield. The reaction with cyano ester **28** gives an intractable polymer, while α-bromo ester **29** does not react at all. Additionally, we have found that polymethylhydrosiloxane does not support a catalytic cycle under the standard conditions when used with this system. This was disappointing, due to the safety concerns associated with the use of triethoxysilane (**SEE WARNINGS**).[46] We have demonstrated that tributoxysilane may be used interchangeably with triethoxysilane, offering a less volatile alternative. Also, it has been recently found that PMHS can be used successfully to reduce esters in combination with substoichiometric amounts (25-50 mol %) of Ti(O-*i*-Pr)$_4$ at higher temperatures (60-80 °C).[48]

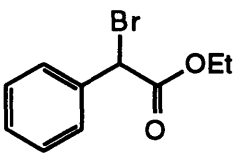
Figure 2



27



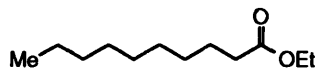
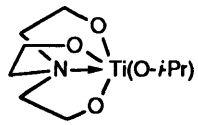
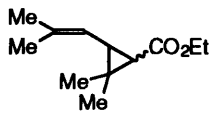
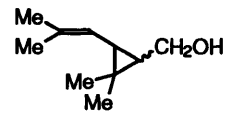
28



29

We have also shown that other early transition metal and lanthanide alkoxides behave as catalysts for ester hydrosilylation. As Table 6 shows, titanium alkoxides are the best reagents for this system in terms of isolated yield, although Nb(OEt)$_5$ (Table 6, entries 1 and 5) also works quite well. Zirconium alkoxides do not behave as catalysts for this reaction, presumably due to the greater strength of the zirconium-oxygen bond.[15] The lanthanide alkoxides (Table 6, entries 2 and 3), while displaying some catalytic turnover, generally require longer reaction times and do not proceed to completion. The isopropoxytitanatrane species[51] (Table 6, entry 4) behaves very similarly to Ti(O-*i*-Pr)$_4$. Structures such as this with stereogenic centers in the carbon backbone may be used to pursue an enantioselective variant of the hydrosilylation system for the reduction of ketones and other prochiral unsaturated compounds.

Table 6. Reduction of Esters Catalyzed by Other Metal Alkoxide Reagents

Entry	Ester	Catalyst[a]	Time (h)	Alcohol	Yield (%)
1		$Nb(OEt)_5$	3		72
2	"	$Nd(O\text{-}i\text{-}Pr)_3$	35	"	24[b]
3	"	$Dy(O\text{-}i\text{-}Pr)_3$	92	"	47[c]
4	"		18	"	87
5		$Nb(OEt)_5$	120		69
6	"	$TiCl_3(O\text{-}i\text{-}Pr)$	168	"	93[d]

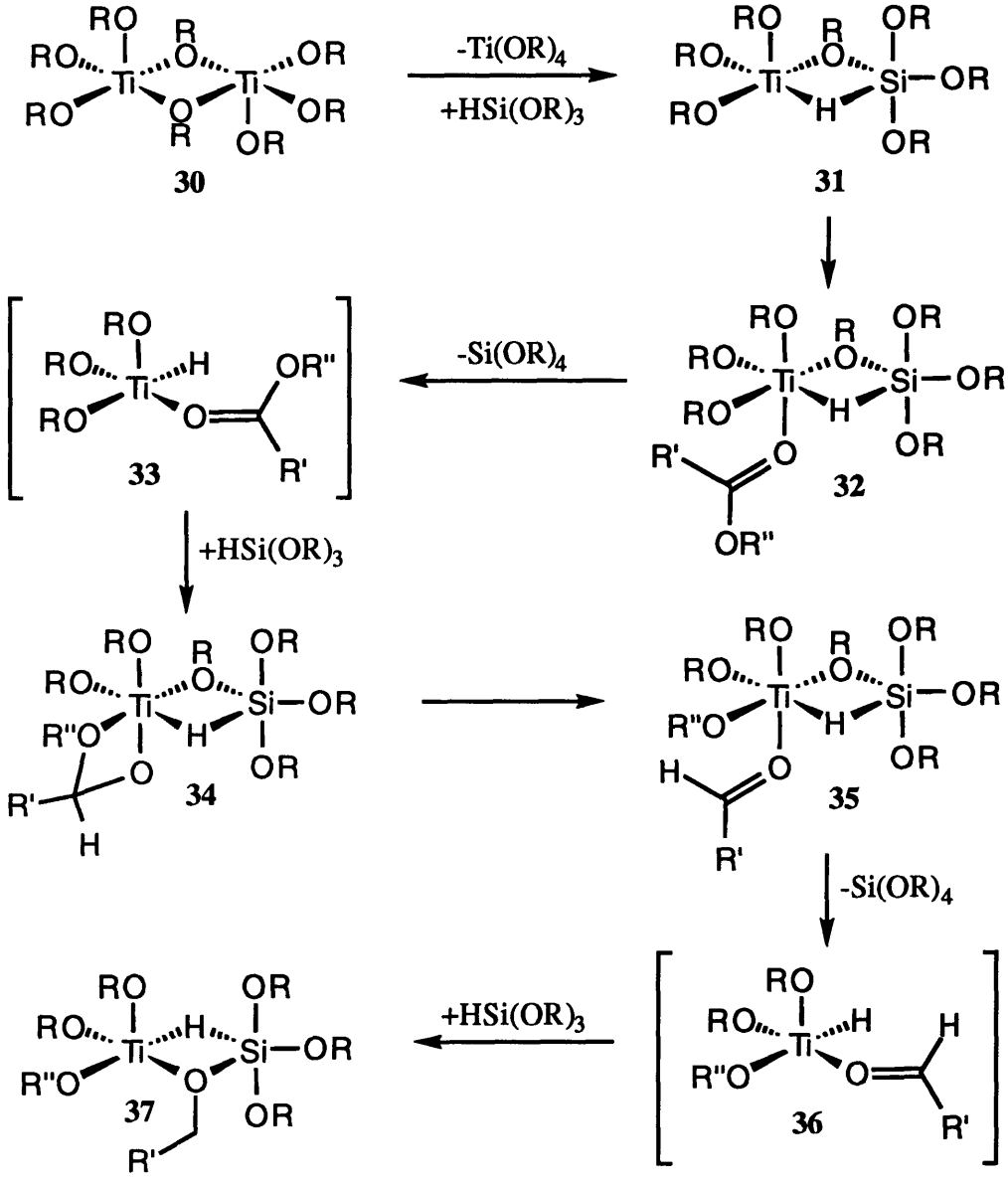
[a]Catalyst loading was 5 mol % in all cases except for entry 6, where loading was 8 mol %. [b]263 mg (44%) of starting material was recovered. [c]40 mg (6%) of starting material was recovered. [d]The product was ~90% pure by ^1H NMR analysis.

We have undertaken several qualitative studies to probe the nature of the active catalyst. One possibility is that this is a simple Lewis acid-catalyzed hydrosilylation, similar to those explored by Calas and Frainnet.[7,8] We have determined that the conversion of ethyl decanoate to decanol is unaffected, in terms of both rate of formation and yield of product, by the addition of 20 equiv (relative to catalyst) of Lewis bases such as pyridine, THF or PMe_3. In a control experiment where $Ti(O\text{-}i\text{-}Pr)_4$ is replaced with the strong Lewis acid, $ZnCl_2$,[7] no reduction is seen under the standard reaction conditions. Another possibility is that the active catalyst is an anionic pentavalent hydridosilicate species, similar to those explored by Corriu and co-workers.[49] These species are known to be electron donors toward organic halides, forming reductive coupling or dehalogenated products. Under our described conditions, ethyl 6-bromohexanoate is converted cleanly to the alcohol with no evidence of dehalogenation. Also, in a control experiment where 1 equiv each of $Ti(O\text{-}i\text{-}Pr)_4$, triethoxysilane, and benzyl bromide were

combined and heated to 45 °C, no 1,2-diphenylethane was detected after two days. Corriu reported a 34% yield of this product under similar conditions starting with $K[HSi(OEt)_4]$.[49] While these results argue against a free hydridosilicate species present in our system, we have observed resonances corresponding to pentavalent alkoxysilanes (δ -81 to -84)[49] in the ^{29}Si NMR spectrum of a 1 : 1 mixture of triethoxysilane and Ti(O-*i*-Pr)$_4$. This indicates that some pentavalent silicon species may be present, perhaps bound to titanium. Finally, we have found that performing the reduction in the presence of 20 equiv (relative to catalyst) of MeI has no effect on the rate or yield of the reaction. Since MeI is expected to trap any free titanium hydride[50] present in the reaction mixture, we are forced to rule out this type of discrete species as the active catalyst as well.

Our mechanistic probes thus far seem to implicate a hybrid species with properties of both a metal hydride and a pentavalent hydridosilicate. One possible catalytic cycle which incorporates this idea is shown in Scheme 12. It is known that titanium alkoxides are dimeric in solution in order to increase their coordination number and become more electron rich.[51] This dimer **30** can dissociate and react with a molecule of silane to form the bridged titanium-hydride/hydridosilicate species **31**. Complexation of the ester to the open coordination site at titanium would form intermediate **32**. Hydride transfer from the silane in exchange for an alkoxide ligand would lead to titanium hydride intermediate **33**, which would be expected to rapidly rearrange and associate with another molecule of silane (again maximizing coordination number) to form **34**. β-Alkoxide elimination could then proceed to form the bound aldehyde complex **35**, which would react in a fashion similar to ester complex **32**. Formation of the intermediate hydride **36**, followed by insertion and re-association with another molecule of silane would then complete the catalytic cycle, forming the new bridged titanium-hydride/hydridosilicate species **37**. Further studies are obviously required to verify this hypothesis.

Scheme 12



In conclusion, we have developed a second generation ester hydrosilylation system which uses air-stable reagents, can be run in the air, and displays a enhanced degree of functional group compatibility. The discovery of this reaction is the result of mechanism-based approach to the optimization of a catalytic cycle. The experimental simplicity and mild reaction conditions of this procedure should make it useful to synthetic chemists, if safety considerations can be overcome. Continued refinement and improvement of the reaction conditions to render the reaction protocol even more attractive are currently underway.

Experimental Section for Chapter 1, Part 2

General Considerations

Unless otherwise indicated, all reactions were conducted in the air, in a dry test tube equipped with a drying tube packed with DrieRite.® All solvents were available from commercial sources and were used directly out of the bottle. Methyl 10,11-epoxyundecanoate, methyl 9,10-epoxyoctadecanoate, and methyl 4-phenyl-3,4-epoxybutyrate were prepared by standard *m*-CPBA oxidation of the corresponding olefins.[38] Methyl 10-undecynoate, methyl 11-hydroxydodecanoate, methyl 2-phenylbutyrate and ethyl 2-chlorobenzoate were synthesized by refluxing the corresponding carboxylic acids in the appropriate alcohol with a catalytic amount of H_2SO_4 for 4-16 h. All other substrates, as well as triethoxysilane, were available from commercial sources and were purified before use by passage through a short column of neutral alumina (ICN Alumina N, Akt I).

Preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230-400 mesh). All products, unless otherwise noted, are commercially available.[36] Yields, unless otherwise stated, refer to isolated yields of compounds of greater than 95% purity as determined by capillary GC and/or ^1H NMR analysis. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, Varian Unity 300, or Bruker AC-250 Fourier transform spectrometer. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; 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 the central line of the 77.0 ppm triplet for deuterochloroform. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 Series Fourier transform spectrometer. Gas chromatography (GC) analyses were performed on a Hewlett Packard model 5890 Gas Chromatograph with a 3392A integrator and FID detector using a 25 m capillary column with crosslinked SE-30 as a stationary phase. Melting points were measured on a Haake Buchler Melting Point Apparatus and are uncorrected.

Titanium (IV) Isopropoxide-Catalyzed Reduction of Esters to Alcohols

General Procedure. Triethoxysilane (1.7 mL, 9.0 mmol) and the ester to be reduced (3.0 mmol) were added to a test tube. Ti(O-*i*-Pr)$_4$ (45 μL, 0.15 mmol, 5 mol %) was then added,[46] and the tube was fitted with a drying tube packed with DrieRite® to exclude excess moisture. The vessel was then heated in an oil bath at 50 °C. The reaction mixture was stirred until all of the starting material was consumed, as determined by GC and/or TLC analysis of an aliquot quenched with a small amount of 1 N NaOH and THF. The reaction mixture was washed into a 100 mL round-bottom flask with 10 mL of THF. Then, 20 mL of 1 N NaOH was added SLOWLY with stirring. (**NOTE:** Vigorous bubbling was observed.) After 4 h, the mixture was added to a separatory funnel with 50 mL each of ether and water. The aqueous layer was separated and extracted with an additional 50 mL of ether. The combined organic extracts were then washed with 2x50 mL of 1 N HCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the desired alcohol. Unless otherwise indicated, the crude product was >95% pure by GC and ^{1}H NMR analysis and was not subjected to further purification.

CAUTION! Adequate eye protection is required for the handling of triethoxysilane (vapors can cause blindness). In the absence of substrate and under inert atmosphere, triethoxysilane is disproportionated by Ti(O-*i*-Pr)$_4$ to form SiH_4, a pyrophoric gas. We have been informed by a user of the procedure that, even in the presence of substrate, running the reaction on a large scale under an inert atmosphere may lead to exotherms and SiH_4 gas production. Therefore, we strongly urge anyone attempting this procedure to run the reaction in the air and to be aware of this possible undesirable side reaction.[46]

Decanol (Table 5, entry 1). The general procedure was followed to reduce ethyl

decanoate (696 μL, 3.0 mmol). After 10 h, work-up (as described) afforded 422 mg (95% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (t, J = 6.4 Hz, 2 H), 1.71 (s, 1 H), 1.57 (m, 2 H), 1.2-1.4 (m, 14 H), 0.88 (t, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.7, 32.7, 31.9, 29.7, 29.6, 29.4, 29.3, 25.8, 22.6, 14.0; IR (neat): 3332, 2915, 2854, 1467, 1378, 1057, 966, 721 cm^{-1}.

2-(2-Thienyl)ethanol (Table 5, entry 2): To a dry round-bottom flask were added triethoxysilane (23.3 mL, 125.0 mmol), ethyl 2-thiophenacetate (7.5 mL, 50.0 mmol), and titanium (IV) isopropoxide (750 μL, 2.5 mmol). The vessel was then fitted with a drying tube packed with DrieRite® and heated in an oil bath at 55 °C. After 4 h, the reaction mixture was washed into a 500 mL round-bottom flask with THF (150 mL). Then, 1 N NaOH (250 mL) was added SLOWLY with stirring. (**NOTE:** Vigorous bubbling was observed.) After 4.5 h of vigorous stirring, the mixture was added to a separatory funnel with 250 mL each of ether and water. The aqueous layer was separated and extracted with 100 mL of ether. The combined organic layers were washed with 2x100 mL of 1 N HCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 5.96 g (93% yield) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 5.0 Hz, 1 H), 6.92 (dd, J = 3.5 Hz, J = 5.0 Hz, 1 H), 6.83 (d, J = 3.5 Hz, 1 H), 3.80 (t, J = 6.4 Hz, 2 H), 3.04 (t, J = 6.4 Hz, 2 H), 2.68 (s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 140.7, 126.8, 125.3, 123.7, 63.1, 33.0; IR (neat): 3332, 3107, 2941, 2874, 1438, 1376, 1244, 1132, 1045, 846, 822, 695 cm^{-1}.

2-Phenyl-1-ethanol (Table 5, entry 3): The general procedure was followed to reduce ethyl 2-phenylacetate (478 μL, 3.0 mmol). After 4 h, work-up (as described) afforded 324 mg (89% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.15-7.35 (m, 5 H), 3.82 (t, J = 7.5 Hz, 2 H), 2.86 (t, J = 7.5 Hz, 2 H), 1.72 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 128.9, 128.4, 126.3, 63.5, 39.1; IR (neat): 3333, 3086, 3060, 3027, 2938, 2877, 1606, 1498, 1451, 1046, 744, 702 cm^{-1}.

6-Bromohexanol (Table 5, entry 4): The general procedure was followed to reduce ethyl 6-bromohexanoate (534 μL, 3.0 mmol). After 6 h, work-up (as described) afforded 476 mg (88% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.62 (t, J = 6.6 Hz, 2 H), 3.40 (t, J = 6.6 Hz, 2 H), 2.99 (s, 1 H), 1.87 (m, 2 H), 1.3-1.6 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 62.2, 33.7, 32.6, 32.4, 27.8, 24.8; IR (neat): 3331, 2936, 2859, 1462, 1430, 1259, 1237, 1052 cm^{-1}.

10-Undecen-1-ol (Table 5, entry 5): The general procedure was followed to reduce methyl 10-undecenoate (594 mg, 3.0 mmol). After 16 h, work-up (as described) afforded 443 mg (87% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (m, 1 H), 4.9-5.05 (m, 2 H), 3.63 (t, J = 6.5 Hz, 2 H), 1.9-2.0 (m, 2 H), 1.63 (s, 1 H), 1.5-1.65 (m, 2 H), 1.2-1.4 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 114.0, 62.8, 33.7, 32.7, 29.5, 29.4 (two overlapping signals), 29.1, 28.9, 25.7; IR (neat): 3336, 3078, 2976, 2933, 2851, 1644, 1465, 1438, 1412, 1059, 990, 911 cm^{-1}.

9-Octadecen-1-ol (Table 5, entry 6): The general procedure was followed to reduce methyl 9-octadecenoate (1.0 mL, 3.0 mmol). After 5 h, work-up (as described) afforded 737 mg (92% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.25-5.4 (m, 2 H), 3.61 (t, J = 6.0 Hz, 2 H), 2.10 (s, 1 H), 1.95-2.05 (m, 4 H), 1.5-1.6 (m, 2 H), 1.1-1.3 (m, 22 H), 0.88 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.9, 129.8, 62.9, 32.8, 31.9, 29.8 (two overlapping signals), 29.5 (two overlapping signals), 29.4 (two overlapping signals), 29.3 (two overlapping signals), 29.2, 27.2, 25.8, 22.7, 14.1; IR (neat): 3331, 3001, 2916, 2855, 1466, 1056, 721 cm^{-1}.

10,11-Epoxyundecan-1-ol (Table 5, entry 7).[39] The general procedure was followed to reduce methyl 10,11-epoxyundecanoate (642 mg, 3.0 mmol). After 21 h, work-up (as

described) followed by flash chromatography (ether : hexane = 1 : 1) afforded 462 mg (83% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (t, J = 6.5 Hz, 2 H), 2.91 (m, 1 H), 2.75 (m, 1 H), 2.45-2.5 (m, 1 H), 1.70 (s, 1 H), 1.2-1.6 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.6, 52.3, 47.0, 32.6, 32.3, 29.3 (two overlapping signals), 29.2 (two overlapping signals), 25.8, 25.6; IR (neat): 3384, 3046, 2922, 2859, 1464, 1412, 1257, 1057, 916, 836, 722 cm^{-1}. Eluting the column with ether : ethyl acetate (3 : 7) afforded 6 mg (1% yield) of a white solid whose ^{1}H NMR spectrum is consistent with its formulation as 1,10,11-undecanetriol: ^{1}H NMR (300 MHz, acetone-d_6): δ 3.3-3.6 (m, 7 H), 2.8 (t, 1 H), 1.2-1.6 (m, 16 H).

9,10-Epoxy-1-octadecanol (Table 5, entry 8).[52] The general procedure was followed to reduce methyl 9,10-epoxyoctadecanoate (624 mg, 2.0 mmol), using triethoxysilane (1.1 mL, 6.0 mmol), and titanium (IV) isopropoxide (30 μL, 0.10 mmol, 5 mol %). After 18 h, work-up (as described), followed by recrystallization from pentane afforded 494 mg (87% yield) of white crystals: m. p.: 52-53 °C (no lit. value reported); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.63 (t, J = 6.6 Hz, 2 H), 2.90 (m, 2 H), 1.2-1.6 (m, 29 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.0, 57.2 (two overlapping signals), 32.8, 31.8, 29.52, 29.50, 29.47, 29.4, 29.3, 29.2, 27.8, 27.7, 26.6 (two overlapping signals), 25.7, 22.6, 14.1; IR (nujol): 3271, 2917, 2851, 1462, 1377, 1074, 846 cm^{-1}.

2-Phenyl-3-hydroxytetrahydrofuran (Table 5, entry 9).[53] The general procedure was followed to reduce methyl 4-phenyl-3,4-epoxybutyrate (576 mg, 3.0 mmol). After 5 h, work-up (as described), followed by purification by flash chromatography (ether : hexane = 1 : 1) afforded 192 mg (39% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2-7.4 (m, 5 H), 4.74 (d, J = 6 Hz, 1 H), 4.05-4.25 (m, 3 H), 2.57 (s, 1 H), 2.05-2.2 (m, 1 H), 1.85-1.95 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 128.4, 127.5, 125.4, 87.5, 78.7, 67.1, 34.0; IR (neat): 3404, 3062, 3030, 2978, 2946, 2885, 1603, 1493, 1452, 1106,

1055, 1028, 992, 911, 735, 700 cm^{-1}.

10-Undecyn-1-ol (Table 5, entry 10). The general procedure was followed to reduce methyl 10-undecynoate (588 mg, 3.0 mmol). After 18 h, work-up (as described) followed by purification by flash chromatography (ether : hexane = 2 : 3) afforded 354 mg (70% yield) of a clear oil: ^1H NMR (250 MHz, $CDCl_3$): δ 3.61 (t, J = 6.6 Hz, 2 H), 2.1-2.2 (m, 3 H), 1.95 (t, J = 2.4 Hz, 1 H), 1.1-1.7 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 83.9, 67.7, 61.8, 32.1, 28.9, 28.8, 28.5, 28.2, 27.9, 25.2, 17.8; IR (neat): 3310, 2927, 2853, 2117, 1466, 1432, 1371, 1350, 1327, 1057, 911, 734, 629 cm^{-1}.

1,12-Dodecanediol (Table 5, entry 11). The general procedure was followed to reduce methyl 12-hydroxydodecanoate (690 mg, 3.0 mmol) using one additional equiv of triethoxysilane (2.1 mL, 11.3 mmol total). After 7 h, work-up (as described) afforded 536 mg (88% yield) of white crystals: m. p.: 82-83 °C (lit.:[36] 81-84 °C); ^1H NMR (300 MHz, acetone-d_6): δ 3.52 (q, J = 6.0 Hz, 4 H), 3.41 (t, J = 6.0 Hz, 2 H), 1.50 (m, 4 H), 1.2-1.4 (m, 16 H); ^{13}C NMR (75 MHz, acetone-d_6): δ 62.6, 34.0, 30.7, 30.6, 30.5, 26.9; IR (nujol): 3407, 3348, 2923, 1461, 1377, 1350, 1058, 1040, 992 cm^{-1}.

Cyclohexylmethanol (Table 5, entry 12). The general procedure was followed to reduce methyl cyclohexanecarboxylate (429 μL, 3.0 mmol). After 16 h, work-up (as described) afforded 300 mg (88% yield) of a clear oil: ^1H NMR (300 MHz, $CDCl_3$): δ 3.44 (d, J = 6.4 Hz, 2 H), 1.99 (s, 1 H), 1.6-1.8 (m, 5 H), 1.4-1.6 (m, 1 H), 1.1-1.35 (m, 3 H), 0.85-1.0 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.5, 40.5, 29.7, 26.7, 25.9; IR (neat): 3331, 2932, 2853, 1449, 1378, 1090, 1034, 892, 734 cm^{-1}.

2-Phenylbutanol (Table 5, entry 13). The general procedure was followed to reduce methyl 2-phenylbutyrate (534 mg, 3.0 mmol). After 14 h, work-up (as described)

afforded 390 mg (87% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15-7.35 (m, 5 H), 3.6-3.8 (m, 2 H), 2.6-2.75 (m, 1 H), 1.5-1.9 (m, 3 H), 1.84 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 128.5, 128.0, 126.5, 67.1, 50.9, 24.9, 12.0; IR (neat): 3355, 3083, 3061, 3027, 2962, 2930, 2874, 1494, 1452, 1379, 1037, 760, 700 cm^{-1}.

1,4-Decanediol (Table 5, entry 14).[54] The general procedure was followed to reduce γ-decanolactone (510 mg, 3.0 mmol). After 16 h, work-up (as described) afforded 454 mg (87% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (s, 1 H), 3.77 (s, 1 H), 3.5-3.7 (m, 3 H), 1.1-1.8 (m, 14 H), 0.88 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.6, 62.6, 37.5, 34.3, 31.8, 29.3, 29.0, 25.7, 22.5, 13.9; IR (neat): 3330, 2927, 2857, 1467, 1378, 1340, 1056, 1014 cm^{-1}.

2-Methoxybenzyl alcohol (Table 5, entry 15). The general procedure was followed to reduce methyl 2-methoxybenzoate (498 mg, 3.0 mmol). After 8 h, work-up (as described) afforded 395 mg (96% yield) of a clear oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.2-7.3 (m, 2 H), 6.8-7.0 (m, 2 H), 4.68 (s, 2 H), 3.86 (s, 3 H), 2.42 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 129.0, 128.9 128.7, 120.6, 110.2, 61.9, 55.2; IR (neat): 3372, 3004, 2939, 1603, 1589, 1493, 1464, 1439, 1289, 1242, 1196, 1116, 1049, 1031, 910, 754, 732 cm^{-1}.

2-Chlorobenzyl alcohol (Table 5, entry 16). The general procedure was followed to reduce ethyl 2-chlorobenzoate (554 mg, 3.0 mmol). After 10 h, work-up (as described) afforded 398 mg (93% yield) of a white solid: m. p.: 70-71 °C (lit.:[36] 69-71 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.4-7.5 (m, 1 H), 7.2-7.4 (m, 3 H), 4.75 (s, 2 H), 2.29 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 132.7, 129.3, 128.7, 128.6, 126.9, 62.7; IR (nujol): 3196, 1362, 1062, 1045, 1034, 990, 750, 701 cm^{-1}.

2-Bromobenzyl alcohol (Table 5, entry 17). The general procedure was followed to reduce ethyl 2-bromobenzoate (684 mg, 3.0 mmol). After 10 h, work-up (as described) afforded 530 mg (95% yield) of a white solid: m. p.: 79-80 °C (lit.:[36] 79-82 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 7.2 Hz, 1 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.28 (t, J = 7.2 Hz, 1 H), 7.15 (t, J = 7.2 Hz, 1 H), 4.67 (s, 2 H), 2.59 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.7, 132.5, 129.0, 128.7, 127.5, 122.4, 64.8; IR (nujol): 3204, 1366, 1056, 1025, 990, 749 cm^{-1}.

Benzyl alcohol (Table 5, entry 18). To a 50 mL round-bottom flask was added methyl benzoate (3.0 g, 37.0 mmol), triethoxysilane (7.4 g, 45.0 mmol), and phenylsilane (4.9 g, 45.0 mmol). Titanium (IV) isopropoxide (570 μL, 1.9 mmol, 5 mol %) was then added, and a drying tube (DrieRite®) was placed over the opening of the flask. The reaction vessel was then heated in an oil bath at 48 °C. After stirring for 10 h, the reaction mixture was washed into a 200 mL round-bottom flask with THF (50 mL). Then, 1 N NaOH (100 mL) was added slowly with stirring. (**NOTE:** Vigorous bubbling was observed.) After 3 h, the mixture was added to a separatory funnel with 150 mL each of ether and water. The aqueous layer was separated and extracted with 2x50 mL of ether. The combined organic extracts were then washed with 3x50 mL of 1 N HCl, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by distillation under reduced pressure (162 °C, ~30 mm Hg) to afford 1.79 g (75% yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1-7.3 (m, 5 H), 4.53 (s, 2 H), 2.92 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 129.0 128.0, 127.5, 65.5; IR (neat): 3320, 3086, 3067, 3030, 2928, 2876, 1496, 1454, 1207, 1026, 1017, 735, 699 cm^{-1}.

4-Nitrobenzyl alcohol (Table 5, entry 19). The general procedure was followed to reduce ethyl 4-nitrobenzoate (586 mg, 3.0 mmol), using triethoxysilane (747 μL, 4.0 mmol), and phenylsilane (520 μL, 4.2 mmol). After 20 h, work-up (as described),

followed by purification by flash chromatography (ether : hexane = 1 : 1) afforded 345 mg (75% yield) of yellow crystals: m. p.: 93-94 °C (lit:[36] 92-94 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (d, J = 10 Hz, 2 H), 7.53 (d, J = 10 Hz, 2 H), 4.83 (s, 2 H), 2.29 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.3, 147.2, 127.0, 123.6, 63.9; IR (nujol): 3516, 2923, 1602, 1507, 1458, 1377, 1342, 1197, 1057, 736 cm^{-1}.

Chrysanthemumyl alcohol (Table 5, entry 20). The general procedure was followed to reduce ethyl chrysanthemumate (650 μL, 3.0 mmol, mixture of *cis* and *trans* isomers), using triethoxysilane (747 μL, 4.0 mmol), and phenylsilane (520 μL, 4.2 mmol). After 22 h, work-up (as described) followed by purification by flash chromatography (ether : hexane = 1 : 1) afforded 370 mg (80% yield) of a pale yellow oil, which was a mixture of *cis* and *trans* isomers in a ratio identical to that of the starting material: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.0-4.9 (m, 1 H, one isomer), 4.9-4.85 (m, 1 H, one isomer), 3.5-3.8 (m, 2 H, both isomers), 1.35-1.75 (m, 7 H, both isomers), 1.38 (m, 1 H, one isomer), 1.0-1.2 (m, 7 H, both isomers), 0.8-0.9 (m, 1 H, one isomer); ^{13}C NMR (62.5 MHz, $CDCl_3$, both isomers): δ 134.7, 132.7, 123.5, 119.1, 63.1, 60.0, 34.9, 30.7, 28.7, 28.5, 26.0, 25.5, 25.4, 22.5, 21.2, 18.2, 18.1, 15.2, two signals obscured by others; IR (neat): 3333, 2921, 1450, 1376, 1122, 1022, 847 cm^{-1}.

Use of Other Metal Alkoxides to Catalyze the Reduction of Esters to Alcohols

Niobium (V) ethoxide

Decanol (Table 6, entry 1). A dry Schlenk tube under argon was charged with $Nb(OEt)_5$ (48 mg, 0.15 mmol, 5 mol %). Triethoxysilane (1.4 mL, 7.5 mmol) and ethyl decanoate (696 μL, 3.0 mmol) were added and the reaction mixture was heated to 50 °C. After 3 h, the reaction was complete, as determined by GC analysis of an aliquot taken from the reaction mixture. THF (8 mL) and 1 N NaOH (15 mL) were then added,

and the mixture was stirred vigorously for 3.5 h. The reaction mixture was then added to a separatory funnel with 50 mL each of H_2O and ether. The aqueous layer was separated and extracted with an additional 50 mL of ether. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (ether : hexane = 1 : 1) afforded 370 mg of a clear oil with a flaky suspension of a precipitate. Filtering the oil through a small plug of celite afforded 343 mg (72% yield) of pure product (>95% pure by ^1H NMR analysis).

Chrysanthemumyl alcohol (Table 6, entry 5). A dry Schlenk tube under argon was charged with $Nb(OEt)_5$ (48 mg, 0.15 mmol, 5 mol %). Triethoxysilane (1.4 mL, 7.5 mmol) and ethyl chrysanthemumate (650 μL, 3.0 mmol) were added and the reaction mixture was heated to 50 °C. After 5 days, the reaction was complete, as determined by GC analysis of an aliquot taken from the reaction mixture. THF (8 mL) and 1 N NaOH (15 mL) were then added, and the mixture was stirred vigorously for 4 h. The reaction was worked up as above. Purification by flash chromatography (ether : hexane = 1 : 1) afforded 320 mg (69% yield) of a yellow oil, a mixture of *cis* and *trans* isomers (>95% pure by ^1H NMR analysis).

Neodymium (III) Isopropoxide

Decanol (Table 6, entry 2). A dry Schlenk tube under argon was charged with $Nd(O\text{-}i\text{-}Pr)_3$ (48 mg, 0.15 mmol, 5 mol %). Triethoxysilane (1.4 mL, 7.5 mmol) and ethyl decanoate (696 μL, 3.0 mmol) were added and the reaction mixture was heated to 60 °C. After 7 h, exposure of the reaction mixture to air caused a flame, presumably due to SiH_4 gas evolution. After 29 h, THF (8 mL) and aqueous 1 N NaOH (15 mL) were added, and the mixture was stirred vigorously for 2.5 h. The reaction was worked up as above. Purification by flash chromatography (ether : hexane = 3 : 7) afforded 114 mg (24% yield) of pure decanol and 263 mg (44% yield) of recovered ethyl decanoate

(both >95% pure by ^{1}H NMR analysis).

Dysprosium (III) isopropoxide

Decanol (Table 6, entry 3). A dry Schlenk tube under argon was charged with Dy(O-*i*-Pr)$_3$ (51 mg, 0.15 mmol, 5 mol %). Triethoxysilane (1.4 mL, 7.5 mmol) and ethyl decanoate (696 μL, 3.0 mmol) were added and the reaction mixture was heated to 60 °C. After 20 h, GC analysis of an aliquot taken from the reaction mixture showed 23% conversion. The reaction mixture was then heated to 70 °C. After an additional 3 days, THF (8 mL) and aqueous 1 N NaOH (15 mL) were added, and the mixture was stirred vigorously for 3 h. The reaction was worked up as above. Purification by flash chromatography (ether : hexane = 3 : 7) afforded 224 mg (47% yield) of decanol (>95% pure by ^{1}H NMR analysis) and 40 mg of recovered ethyl decanoate (84% pure, 5.5% yield).

(2-Propanolato)titanatrane[51]

Decanol (Table 6, entry 4). Triethoxysilane (1.4 mL, 7.5 mmol) and ethyl decanoate (696 μL, 3.0 mmol) were added to a dry test tube. (2-Propanolato)titanatrane (38 mg, 0.15 mmol, 5 mol %) was then added, and the tube was fitted with a drying tube packed with DrieRite® to exclude excess moisture. The vessel was then heated in an oil bath at 50 °C. After 18 h, the reaction mixture was washed into a 100 mL round-bottom flask with 10 mL of THF. Then, 20 mL of 1 N NaOH was added SLOWLY with stirring. (**NOTE:** Vigorous bubbling was observed.) After 4 h, the mixture was added to a separatory funnel with 50 mL each of ether and water. The aqueous layer was separated and extracted with an additional 50 mL of ether. The combined organic extracts were then washed with 2x50 mL of 1 N HCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 412 mg (87% yield) of decanol (>95% pure by ^{1}H NMR analysis).

Titanium (IV) Trichloroisopropoxide

Chrysanthemumyl alcohol (Table 6, entry 6). Triethoxysilane (1.4 mL, 7.5 mmol) and ethyl chrysanthemumate (650 μL, 3.0 mmol) were added to a dry test tube. $TiCl_3$(O-*i*-Pr) (35 mg, 0.25 mmol, 8 mol %) was then added, and the tube was fitted with a drying tube packed with DrieRite® to exclude excess moisture. The vessel was then heated in an oil bath at 40 °C. After 7 days, the reaction was complete as determined by GC analysis of an aliquot taken from the reaction mixture. THF (7 mL) and aqueous 1 N NaOH (15 mL) were then added, and the mixture was stirred vigorously for 2 h. The reaction was worked up as above to afford 429 mg (93% yield) of crude product which was >90% pure by ^{1}H NMR analysis.

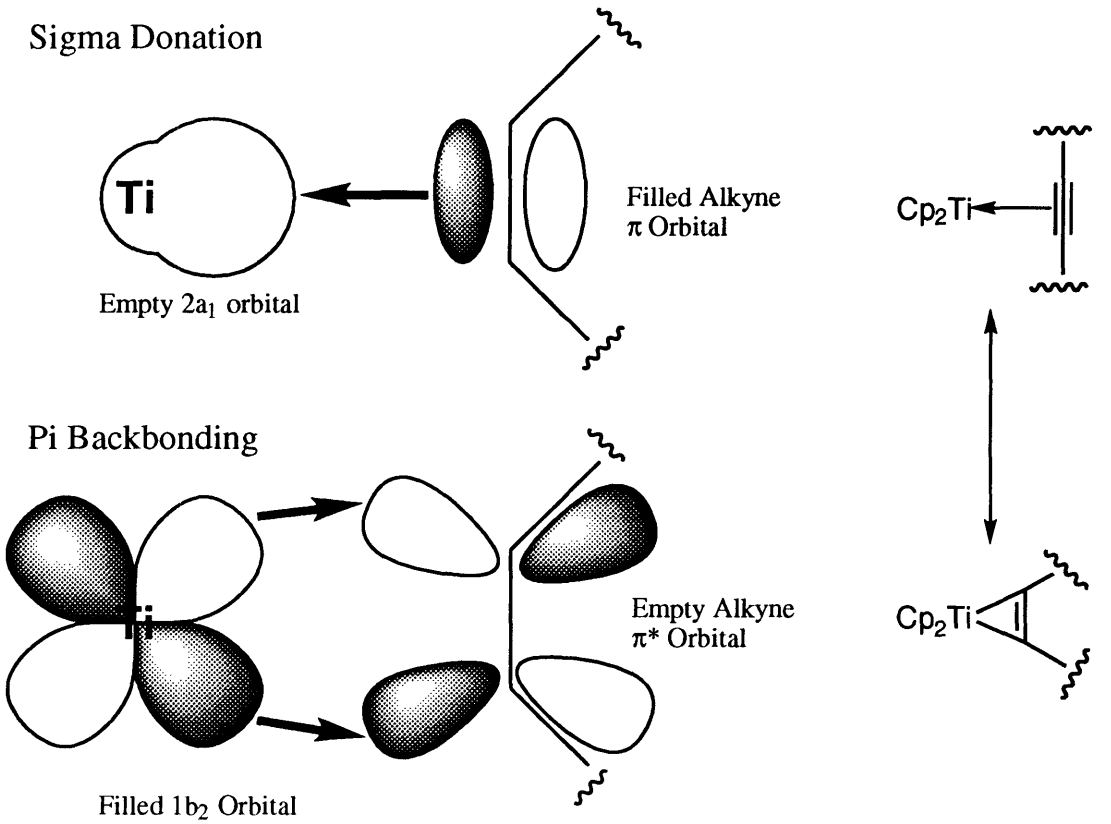
CHAPTER 2

DEVELOPMENT OF A TITANOCENE-CATALYZED REACTION TO CONVERT ENYNES TO BICYCLIC CYCLOPENTENONES

Background

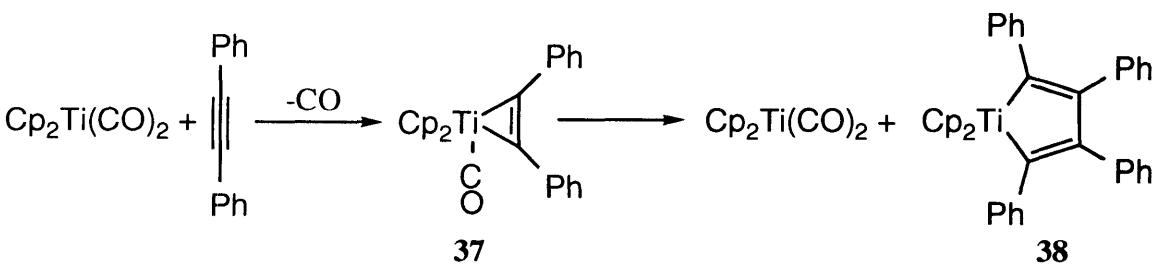
One of the more interesting features of organometallic reagents is their ability to mediate reactions which are difficult or impossible using classical methods of organic synthesis. One example is the activation of simple unsaturated organic fragments by group 4 metallocene compounds, a process which has been studied in some detail.[55] An alkyne complex of zirconocene or titanocene follows the Dewar-Chatt-Duncanson model of bonding.[56] According to this model, there are two interactions which occur when an alkyne binds to the metal (see Figure 3). The first is σ-donation of a filled alkyne π orbital into the empty $2a_1$ molecular orbital of the metallocene.[57] The second is π backbonding from the filled $1b_2$ orbital of the metallocene into the empty π^* antibonding orbital of the alkyne. Thus, there are two extreme resonance forms of a group 4 metallocene alkyne complex, as indicated in Figure 3. The reactivity of these 16-electron complexes resembles that of a metallacyclopropene, and a 1,2-insertion of another unsaturated organic fragment can easily occur in what has been termed a "reductive coupling" reaction.

Figure 3



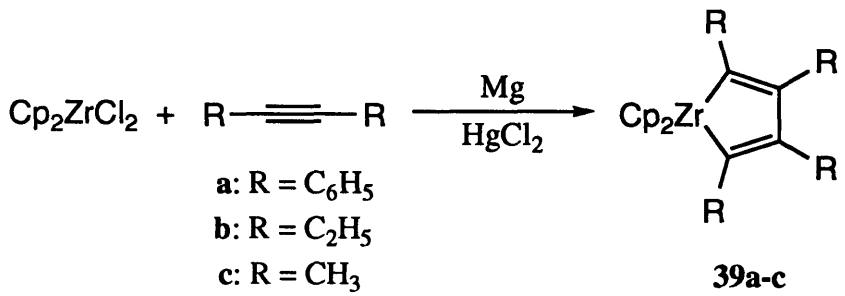
Floriani and co-workers[58] were able to prepare the alkyne complex **37** from the reaction of the "titanocene" equivalent, $Cp_2Ti(CO)_2$, with diphenylacetylene (Scheme 13). They also showed that **37** disproportionates over time to form $Cp_2Ti(CO)_2$ and **38**. The structure of intermediate **37** was determined from an X-ray analysis. The carbon-carbon bond of the alkyne was found to be significantly lengthened (1.285 Å; average length of a C-C triple bond is 1.2 Å), and the phenyl groups were bent back from the linear arrangement (C-C-C bond angle: 145.8°). Thus, in the solid state, complex **37** most closely resembles a metallacyclopropene.

Scheme 13



37 **38**

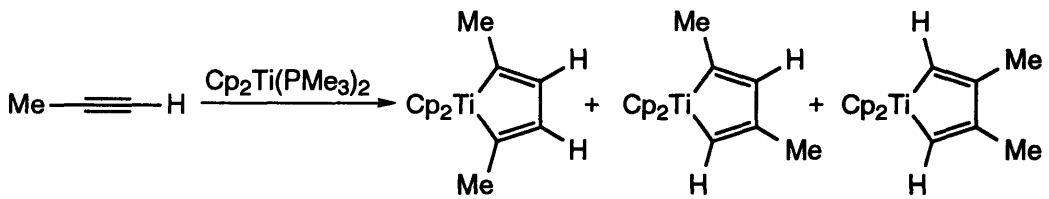
In a further development, Farona and co-workers[59] demonstrated the use of a zirconocene equivalent, generated by the $Mg/HgCl_2$ reduction of Cp_2ZrCl_2, to synthesize a series of substituted metallacyclopentadienes **39a-c** from the reductive coupling of symmetrical alkynes (eq 12). It is important to note that, up to this point, only symmetric alkynes had been used for the reaction. Alt, Rausch and co-workers[60] demonstrated the use of a new phosphine-stabilized titanocene reagent, $Cp_2Ti(PMe_3)_2$, to reductively couple several terminal alkynes. They reported that this reaction was not very selective, leading to mixtures of regioisomers (eq 13). Indeed, the lack of regioselectivity and the problems associated with the cross-coupling of two different unsaturated compounds was a major shortcoming of this method towards its application in organic synthesis.



a: R = C_6H_5
b: R = C_2H_5
c: R = CH_3

39a-c

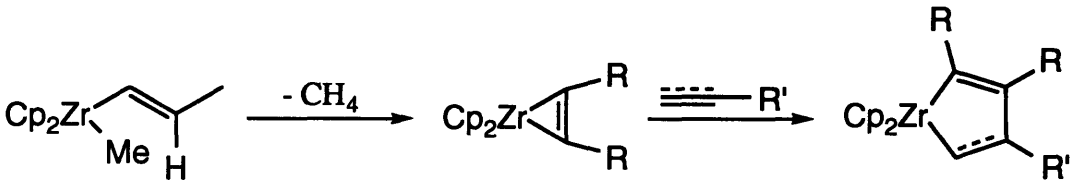
(12)



(13)

There have been two solutions to this problem which have led to the use of the reductive coupling reaction in a variety of novel organic methodologies. One method, pioneered in the Buchwald laboratories,[61] involves the formation of a reactive zirconocene alkyne complex **41** from compounds of type **40** by the concerted loss of an alkane (usually methane) via a β-hydrogen abstraction process. When this reaction is performed in the presence of a suitable unsaturated organic fragment, reductive coupling can occur to give metallacycles of type **42** (Scheme 14).

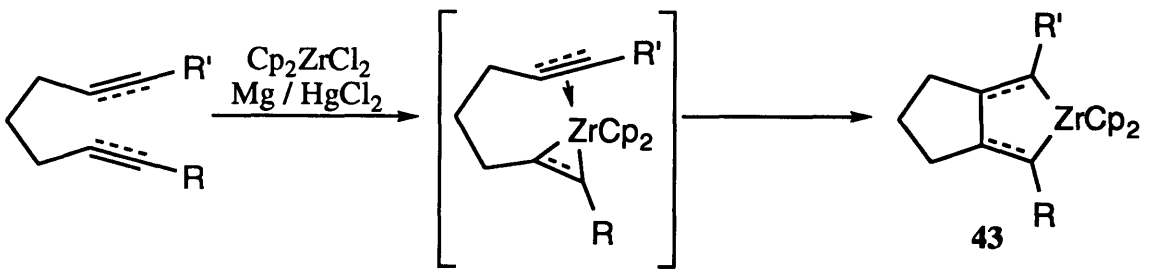
Scheme 14



40 **41** **42**

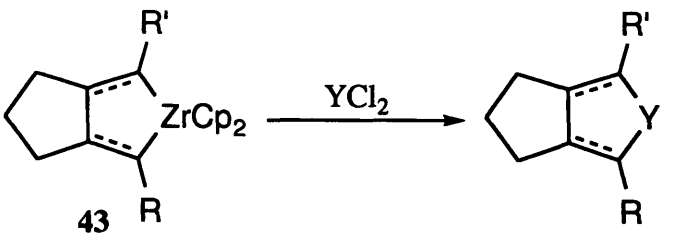
The second strategy, developed by Nugent and co-workers, was to form bicyclic metallacycles **43** directly by *in situ* generation of the active metallocene reagent in the presence of a diyne,[62] enyne,[63] or diene (Scheme 15).[64] In most cases, the intramolecular reductive coupling reaction occurs before dimerization or oligomerization. The metallacycles **42** and **43** behave as 1,2-dianion equivalents, and have been shown to react with electrophiles[61,65] to furnish a host of highly functionalized organic compounds and organo-main group compounds (Scheme 16). More recently, other researchers have applied Nugent's method to the intramolecular cyclization of hydrazone/alkenes (or alkynes),[66] enones and ynones.[67]

Scheme 15



43

Scheme 16

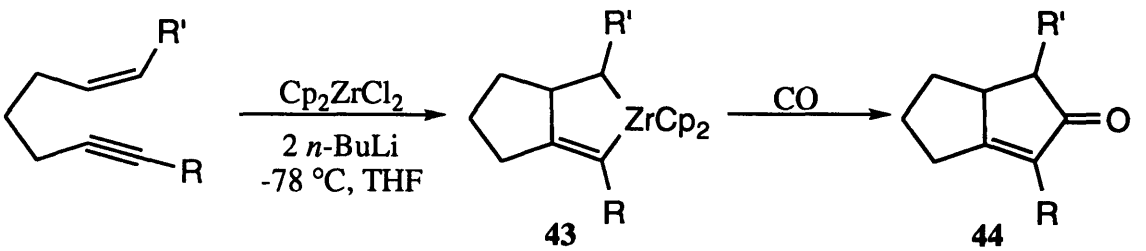


43

Y = (H, H), PPh, AsPh, SbPh, BiPh, $GeCl_2$, $InCl_2$, S, Se, $SnMe_2$, S=O, B-R

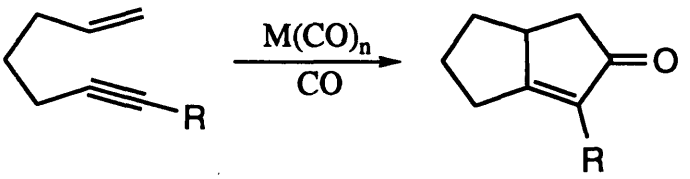
Negishi and co-workers discovered an entry into a zirconocene species which greatly increased the synthetic utility of the intramolecular reductive coupling reaction. They found that zirconacycles of type **43** could be generated by the reaction of Cp_2ZrCl_2 with 2 equiv of *n*-BuLi[68] at low temperature, followed by addition of dienes, diynes, or enynes and warming to room temperature. The procedure is experimentally much simpler than the previous method (reduction of Cp_2ZrCl_2 with $Mg/HgCl_2$[59]). The Negishi group also showed that the zirconacycles could be directly carbonylated[69] to produce, in a one pot procedure, bicyclic cyclopentenones **44** (Scheme 17). This method provides an easy way to prepare cyclopentenone skeletons from simple starting materials, and has been used successfully as the key step of several natural product syntheses.[70]

Scheme 17

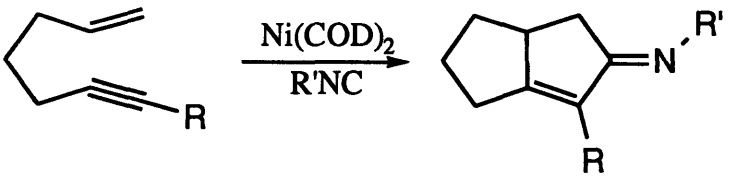


The metal-induced conversion of enynes to bicyclic cyclopentenones was not unprecedented. Carbonyl complexes of cobalt[71] (the intramolecular Pauson-Khand reaction), iron[72] and tungsten[73] had also been shown to effectively mediate this transformation. Additionally, Tamao has used bis(cyclooctadienyl) nickel in the presence of an isocyanide, used as a carbon monoxide equivalent, to convert enynes to bicyclic iminocyclopentenes (Scheme 18).[74] Note that in each case, a stoichiometric amount of the metal species is required to effect the desired transformation.[75]

Scheme 18

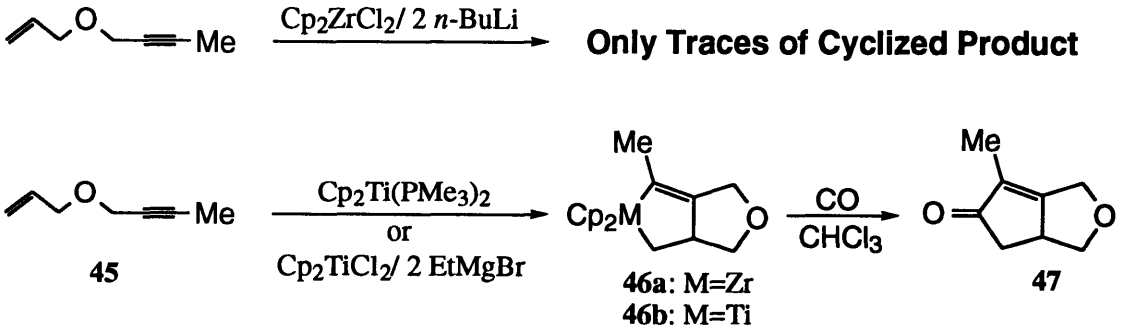


$M(CO)_n = Co_2(CO)_8$, $Fe(CO)_4$, $W(CO)_5$•THF



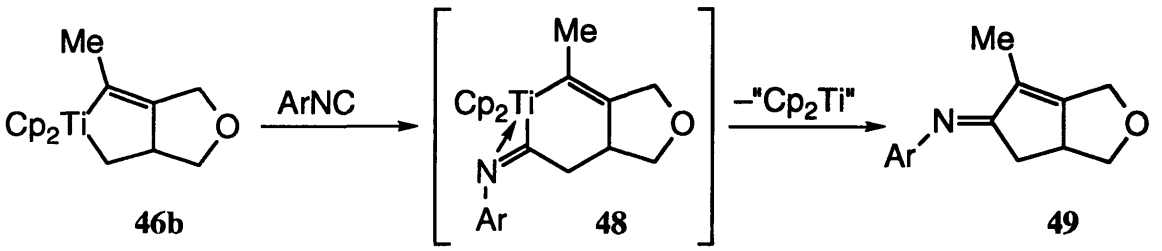
While attempting to use Negishi's method to synthesize cyclopentenone **47**, Robert Grossman was surprised to find that the cyclization of enyne **45** provided only a trace of the desired zirconacycle **46a** (Scheme 19).[76] He thought that this may due to an irreversible interaction between the oxygen atom and zirconium. Because titanium-oxygen bonds are substantially weaker than zirconium-oxygen bonds (by ~20 kcal/mol),[15] Grossman attempted the reaction using $Cp_2Ti(PMe_3)_2$[11] and was able to generate the metallacycle **46b** quantitatively. Direct carbonylation in chloroform afforded the desired product **47**. Grossman discovered that the combination of Cp_2TiCl_2 and 2 equiv of EtMgBr (or *n*-BuLi) functioned similarly to the analogous zirconium system as an *in situ* generated titanocene equivalent. Unlike the zirconium reaction, the titanium mediated cyclization also tolerated the presence of ester groups.[76,77]

Scheme 19



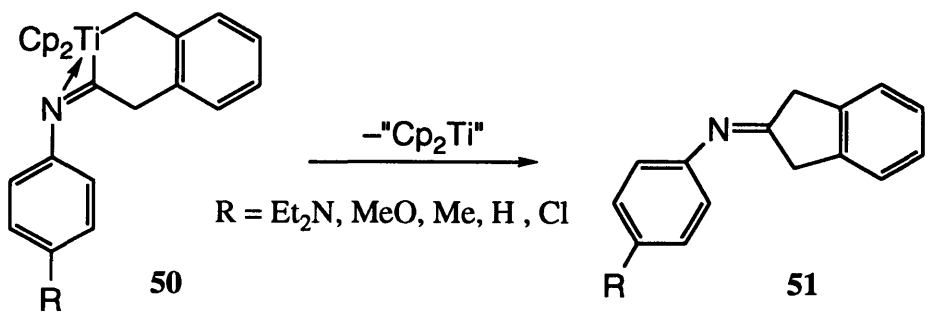
Grossman also showed that the addition of 2,6-dimethylphenylisocyanide to metallacycle **46b** led to the expected 1,1-insertion into the titanium-sp^3 carbon bond, providing iminoacyl compound **48** (Scheme 20).[78] Over time, this complex decomposed, presumably *via* the reductive elimination of "titanocene", to form the bicyclic iminocyclopentene **49** in good yield.[76]

Scheme 20



46b **48** **49**

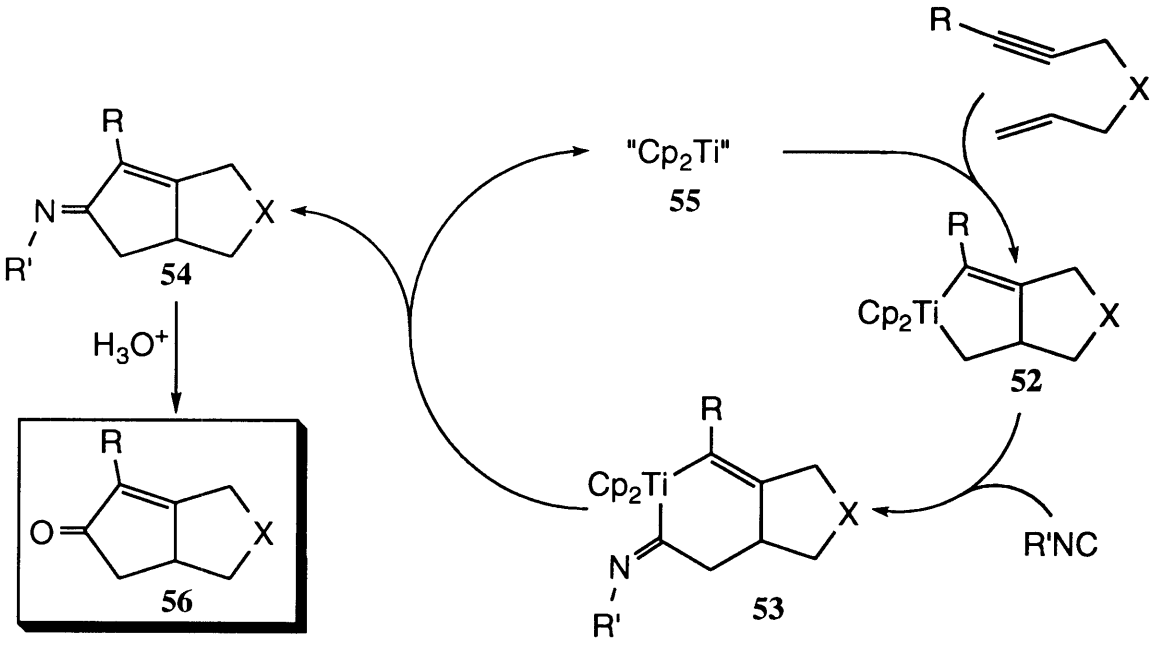
While there was precedent for this type of reductive elimination reaction,[79] it had not been the subject of careful study. Juan Cámpora monitored the rates of decomposition of a series of titanocene iminoacyl complexes **50** to the corresponding imines **51** (eq 14).[80] He found that the decomposition reaction displayed first-order kinetics and was unaffected by the addition of donor ligands such as PMe_3. The rate of elimination was accelerated by the presence of electron withdrawing substituents on the N-phenyl ring (ρ value from a Hammet plot = +1.55) and was slightly decelerated in the presence of polar solvents. Most importantly for our purposes, he was able to trap the eliminated "Cp_2Ti" fragment with dimethyldisulfide, demonstrating that the titanocene reagent was not destroyed in the reductive elimination.



50 **51** **(14)**

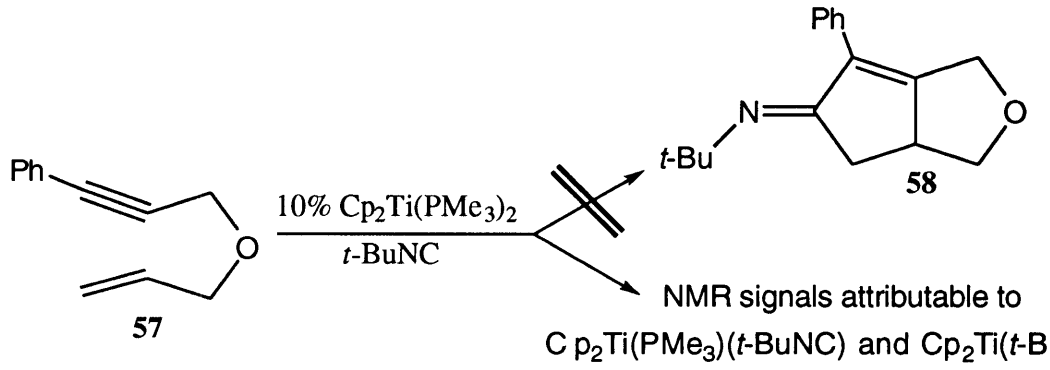
Cámpora's result led us to envision the catalytic cycle shown in Scheme 21. After isocyanide insertion into the bicyclic metallacycle **52** to form iminoacyl complex **53**, reductive elimination reaction would provide bicyclic iminocyclopentene **54** and reactive "titanocene" species **55**. If this reactive fragment could be trapped by another equivalent of enyne prior to its decomposition or conversion to "dead end" products, the cycle would be completed. Hydrolysis of imine **54** would then furnish bicyclic cyclopentenone **56**. Thus, we began our efforts to devise the proper conditions to render the process catalytic.[81]

Scheme 21



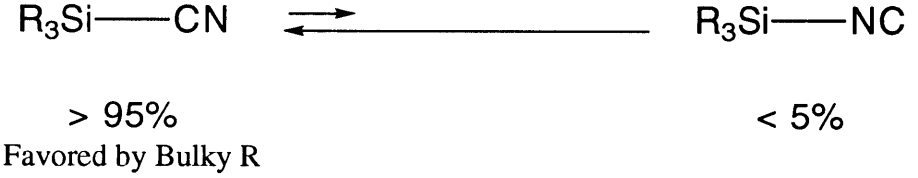
Results and Discussion

Attempts to cyclize enyne **57** using 10 mol % of $Cp_2Ti(PMe_3)_2$ in the presence of *t*-butylisocyanide proved fruitless. ^1H NMR analysis showed no reaction of the enyne and resonances attributable to isocyanide complexes of titanocene (eq 15).[82] Evidently, the titanocene reagent reacts much faster with the isocyanide than with the enyne. Efforts to limit the concentration of isocyanide by slow or portionwise addition resulted in little improvement. Sequential addition of enyne and *t*-butylisocyanide to a stoichiometric amount of $Cp_2Ti(PMe_3)_2$, repeated four times, gave a 220% yield (by ^1H NMR analysis) of **58** based on titanium,[76b] suggesting that catalytic turnover was indeed possible.



(15)

We saw a potential solution to the "isocyanide delivery" problem in the interesting tautomeric equilibrium which exists between trialkylsilylcyanides and the corresponding isocyanides (eq 16).[83] The equilibrium largely favors the cyano tautomer (~95:5 in the case of trimethylsilylcyanide). Furthermore, the "normal : iso" ratio can be affected by modifying the nature of the groups on the silicon. We hoped that running the reaction in the presence of the appropriately substituted trialkylsilylcyanide would be an ideal way to conveniently limit the concentration of free isocyanide in the reaction mixture.

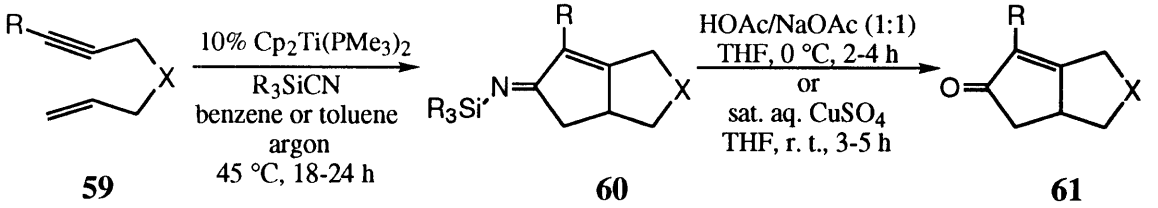


(16)

After much experimentation, it was found that 10 mol % of $Cp_2Ti(PMe_3)_2$, under the conditions shown in Scheme 22, would catalytically convert enynes **59** and a slight excess of trialkylsilylcyanide to the corresponding iminocyclopentenes **60**. Use of Me_3SiCN gave variable results, although in some cases complete consumption of the enyne was observed when slow addition of the silyl cyanide was employed (Table 7, entries 1, 2 and 4). Reactions employing *i*-Pr_3SiCN went to completion, but were too slow to be useful (10 days, r.t.). *t*-$BuMe_2SiCN$ proved to be a good compromise with respect to both reactivity and compatibility. Reactions employing *t*-$BuMe_2SiCN$ generally were run at 45 °C for 18-24 hours (Table 7, entries 4-7, 10 and 12). One drawback of this reagent is that it is a waxy solid and difficult to prepare in a pure form. More recently, we found that Et_3SiCN, an easily distillable liquid, works well under the standard reaction conditions (Table 7, entries 3, 7-9, 11 and 13). Another advantage of Et_3SiCN is that reaction times using this reagent are slightly shorter (12-16 hours, 45 °C).

For certain substrates (Table 7, entries 9, 11 and 12), greater than 10 mol % of catalyst is required for complete conversion. This effect is probably steric in origin. With these bulkier enynes, binding to the titanocene species **55** is more difficult, and with each turnover of the cycle (see Scheme 21), there is a greater chance that **55** will decompose before metallacycle **52** can form.

Scheme 22



59 **60** **61**

Table 7. Titanocene-Catalyzed Conversion of Enynes to Bicyclic Cyclopentenones

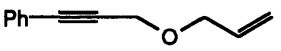
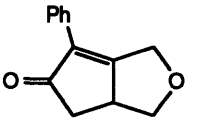
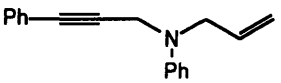
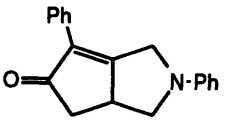
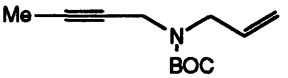
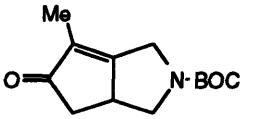
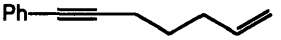
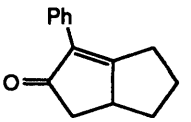
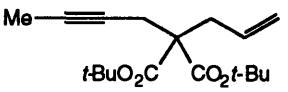
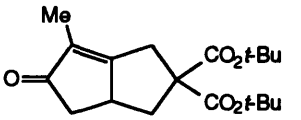
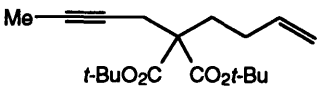
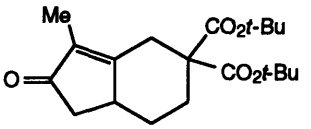
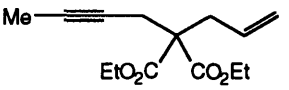
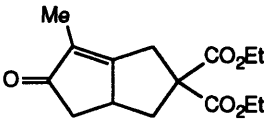
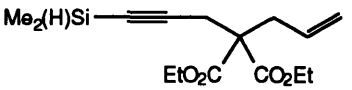
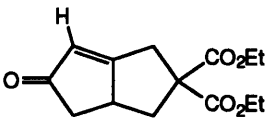
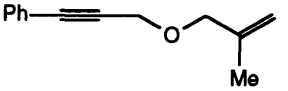
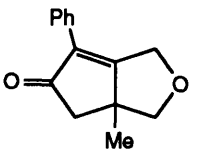
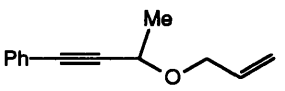
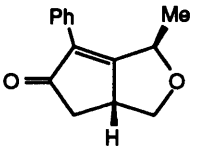
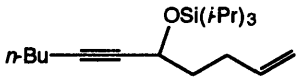
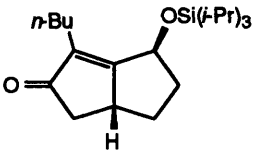
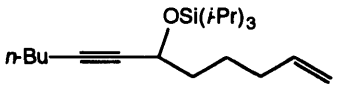
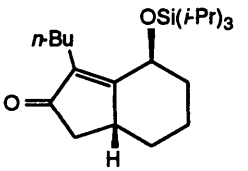
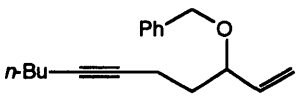
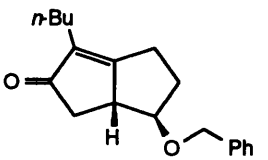
entry	starting material	cyanide[a]	product	isolated yield (%)[d]
1		Me_3SiCN		80
2		Me_3SiCN		44[b]
3		Et_3SiCN		43
4		Me_3SiCN t-$BuMe_2SiCN$		55 66
5		t-$BuMe_2SiCN$		70
6		t-$BuMe_2SiCN$		71
7		t-$BuMe_2SiCN$ Et_3SiCN		65 71
8		Et_3SiCN		42
9		Et_3SiCN[c]		58

Table 7 (cont.)

entry	starting material	cyanide[a]	product	isolated yield (%)[d]
10		*t*-BuMe$_2$SiCN		71 (5 : 1)
11		*t*-BuMe$_2$SiCN[e]		54 (1.6 : 1)
12		*t*-BuMe$_2$SiCN[e]		52[f]
13		Et_3SiCN		45 (12 : 1)

[a]Me_3SiCN was added slowly over a 4–8 h period; *t*-BuMe$_2$SiCN and Et_3SiCN were added immediately at the beginning of the reaction. See Experimental Section for full details. [b]13% of starting material was also isolated. [c]Required 20 mol % catalyst for complete reaction. [d]The major isomer, as assigned on the basis of NOE analysis, is shown. Numbers in parentheses indicate the ratio of diastereomers. [e]Required 15 mol % catalyst for complete reaction. [f]The isomer shown was the only one detected.

In all cases shown in Table 7, conversion of enyne **59** to imine **60** was nearly quantitative (^{1}H NMR analysis). Hydrolytic workup of **60** was the yield limiting step, affording cyclopentenones **61** in fair to good yield.[84] The cyclization reaction successfully forms both 5,5- and 5,6-fused ring compounds, and tolerates the presence of polar functional groups, such as ethers (Table 7, entries 1 and 9-13), nitrogen-containing compounds (Table 7, entries 2 and 3), and esters (Table 7, entries 5-8). This is similar to the functional group toleration which we have observed in the stoichiometric reactions.[76]

For the cyclization of enynes containing stereogenic centers (Table 7, entries 10-13), levels and sense of diastereoselectivity for this process were similar to those observed in related zirconium-mediated stoichiometric processes reported by Nugent and Livinghouse.[63,85] There is a large degree of 1,3-stereoinduction for the formation of 5,6-fused ring systems (Table 7, entry 12). While ^{1}H NMR analysis of the intermediate imines shows a small amount (< 10%) of the minor diastereomer, the ketone shown in Table 7, entry 12 was the only diastereomer detected after hydrolysis. Livinghouse has rationalized this selectivity on the basis of the reduction of allylic 1,3-strain in the pre-cyclization conformers (Figure 4).[85] No explicit explanation was given for the observed selectivity for the formation of 5,5-fused systems. MM2 molecular modeling (using an augmented parameter set for use with metal complexes) shows that the observed selectivity in these cases can be explained as a result of the reduction of 1,3-diaxial interactions in the pre-cyclization conformers (Figure 5). While high 1,2-stereoinduction is observed (Table 7, entry 12), only modest 1,3-stereoinduction is seen (Table 7, entries 10 and 11),[63] perhaps due to competing allylic 1,3-strain (see Figure 6).

Figure 4

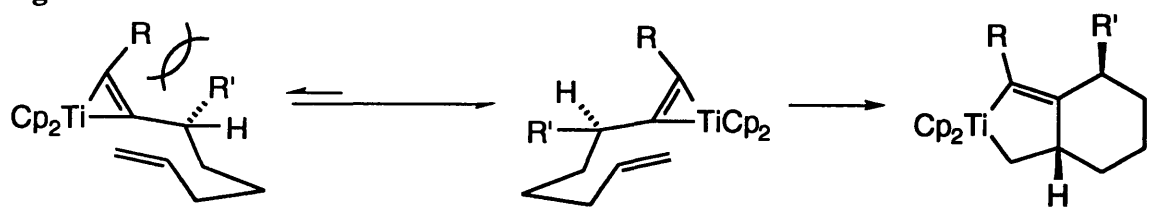


Figure 5

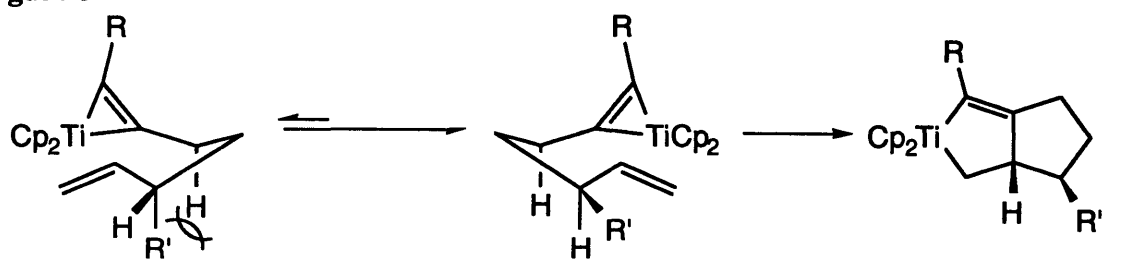
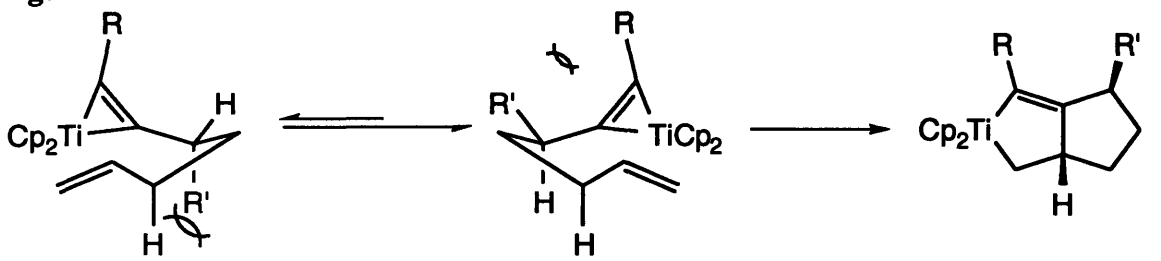
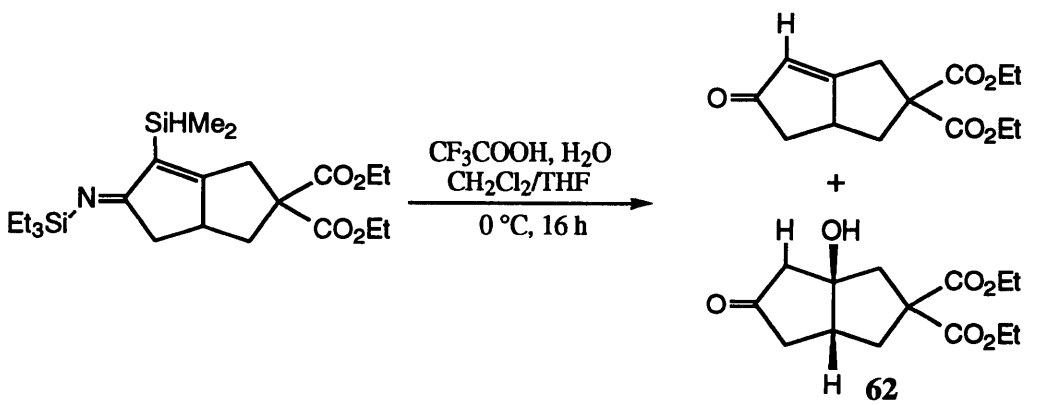


Figure 6



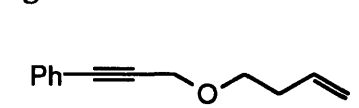
Much attention was devoted to the improvement of the hydrolysis procedure, with mixed results. Under a variety of conditions, ranging from acidic to alkaline, significant amounts of the product were decomposed through tautomerization, enamine formation, and polymerization. For several substrates, a significant amount of β-hydroxy alcohol, formed by Michael addition of water to the cyclopentenone (or imine), was shown to be present in the crude reaction mixture. For entry 8 of Table 7, the alcohol product **62** was isolated as a pure material in 22% yield and characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy (eq 17). The two best hydrolysis procedures to date are shown as part of Scheme 22. We have found that the $CuSO_4$ work-up protocol is somewhat useful for substrates where the determination of diastereoselectivity is a concern. The acidic conditions of the acetic acid/sodium acetate work-up procedure epimerize the stereogenic center at C-5, leading to false product diastereomer ratios (this was seen for Table 7, entry 13 and led to a decreased diastereomer ratio of 3 : 1). For the product in Table 7, entry 8, trifluoroacetic acid is required to remove the silyl group through a protodesilylation reaction (eq 17).



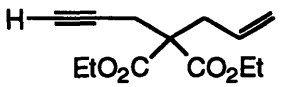
(17)

Several substrates which resist catalytic cyclization are listed in Figure 7. The enyne ether **63**, which cyclizes to form a 5,6-fused ring system with oxygen in the backbone, does not turn over catalytically under the standard reaction conditions. However, **63** can be converted to the corresponding iminocyclopentene using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$. Further optimization of the silyl cyanide reagent may lead to catalytic activity with this substrate. Terminal alkyne **64** was also not successfully cyclized under catalytic conditions. This result was not surprising, since it has been shown that terminal alkynes do not cyclize using stoichiometric titanium or zirconium reagents, attributed to a side reaction with the acidic alkyne proton.[63] Enyne ethers **65** and **66** each contain a 1,2 disubstituted olefin. These substrates do not cyclize, even under stoichiometric conditions. Examination of molecular models of the corresponding metallacycle shows a severe steric interaction between the terminal olefin substituent and the cyclopentadienyl rings on the titanium. Silane **67** does not cyclize intramolecularly. Instead, it forms the dimer **68**, implying that the required geometry of the desired 5,5-fused bicyclic species is inaccessible. The enyne in Table 7, entry 12 requires 15 mol % of catalyst to effect complete cyclization. Thus, enyne **69** was prepared with the hope that the Thorpe-Ingold effect[86] would render the cyclization of this type of substrate more favorable. Unfortunately, **69** was actually a worse substrate for the cyclization reaction. Substrates **70** and **71**, containing carbonyl groups within the tether between the alkyne and olefin units, led to a complex mixture of products by ^1H NMR. No iminocyclopentene was observed, possibly due to side reactions arising from the formation of titanocene-carbonyl complexes. Grossman has shown that substrates of this type do not cyclize well using the stoichiometric system.[76]

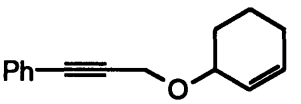
Figure 7



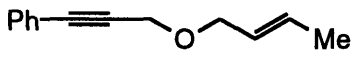
63



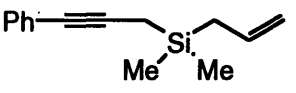
64



65



66



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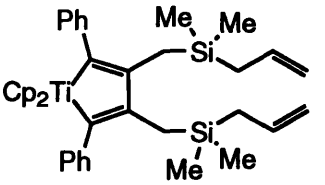

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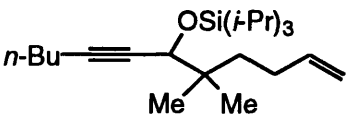

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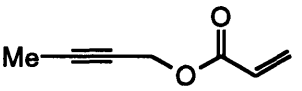

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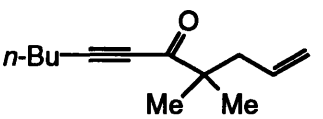
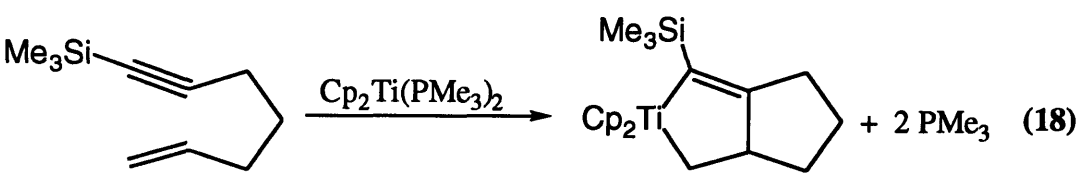
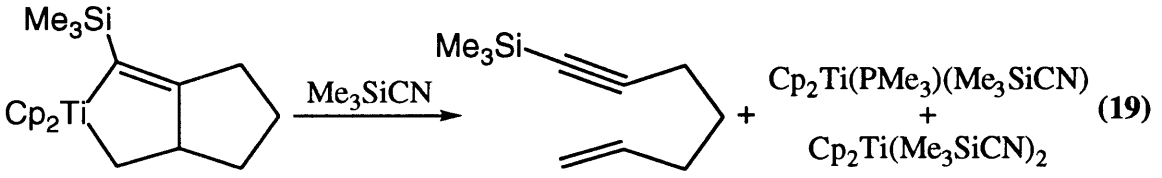


71

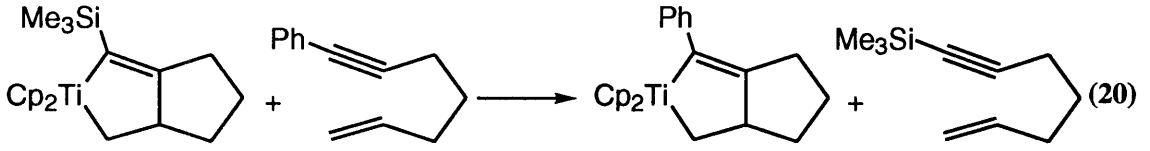
When the trimethylsilyl substituted enyne **72** failed to cyclize under catalytic conditions, we reasoned that the corresponding titanacycle, **73**, may not be stable. We tried the reaction using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$, and found that **73** was formed cleanly in high yield, and could be isolated as an air-sensitive solid (eq 18). Treatment of **73** with Me_3SiCN, *t*-butylisocyanide, or even acetonitrile, resulted in a retro-cyclization reaction to give back the trimethylsilyl enyne (eq 19) along with isocyanide complexes of titanocene. Combining titanacycle **73** with an enyne that is a good substrate under catalytic conditions, such as **74**, led to an enyne exchange reaction to provide the trimethylsilyl enyne and the new metallacycle **75** (eq 20). The rate of this reaction is doubled in the presence of a good donor ligand, such as PMe_3.



72 **73**



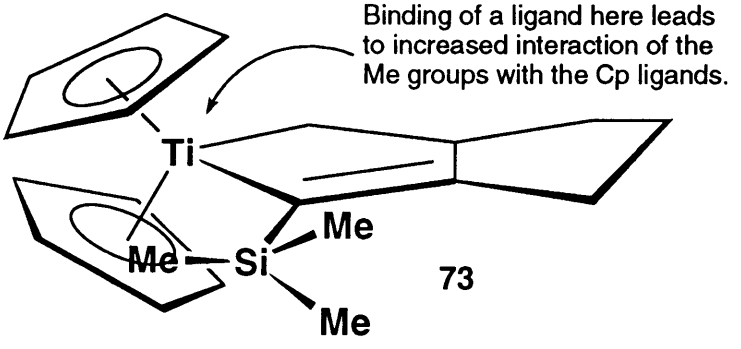
73 72



73 74 75 72

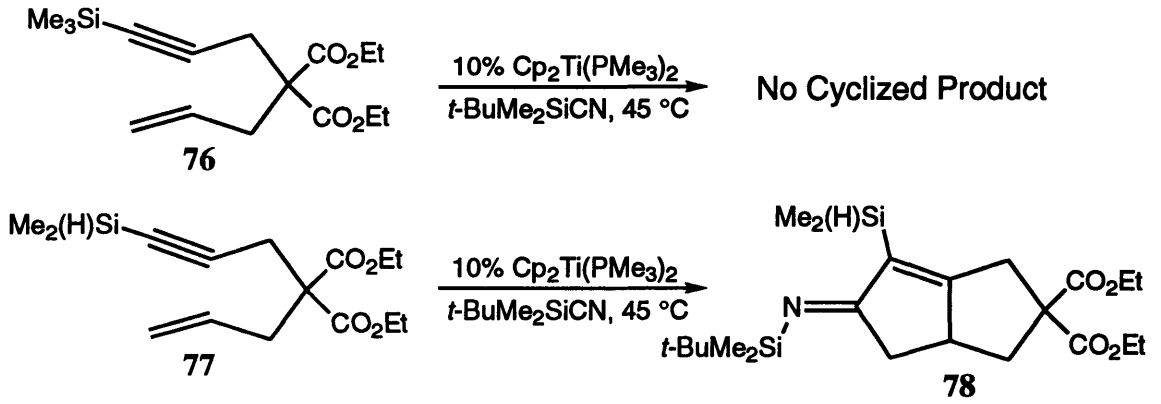
Examination of molecular models of **73** showed that the trimethylsilyl group is very close to the cyclopentadienyl ligands (see Figure 8). When a ligand binds to this complex, we believe the steric environment around the metal becomes severely crowded, and the resulting strain causes the retro-cyclization reaction to become energetically favorable. This may explain why the enyne exchange reaction is ligand accelerated. To test this hypothesis, enynes **76** and **77** were subjected to the standard reaction conditions. While the trimethylsilyl substituted enyne did not react, **77** reacted smoothly to afford bicyclic iminocyclopentene **78** quantitatively (Scheme 23).

Figure 8



73

Scheme 23



In conclusion, we have developed the first early transition metal system for the catalytic formation of bicyclic cyclopentenones from enynes and a carbon monoxide equivalent. The reaction is tolerant of polar functional groups and cyclizes chiral enynes with a moderate to good degree of diastereoselectivity. While we have made a considerable amount of progress in the development of the reaction, we are continuing our efforts to improve the yields, substrate compatibility, and experimental simplicity. We note that while all of the entries in Table 7 were cyclized using 10 mol % of highly air-sensitive $Cp_2Ti(PMe_3)_2$, we have been able to generate an active catalyst *in situ* from Cp_2TiCl_2 and 2 equiv per catalyst of *n*-BuLi. Running the reaction with 20 mol % catalyst loading is necessary to ensure complete conversion of the enyne. Future work will be directed towards further refining the *in situ* generated catalyst system and toward the development of enantiopure catalysts of titanium and other metals.

Experimental Section for Chapter 2

General Considerations

All manipulations involving air sensitive materials were conducted in a Vacuum Atmospheres Dry Box or by using standard Schlenk techniques under an atmosphere of argon. THF and benzene were distilled under argon from sodium/benzophenone ketyl before use. Toluene was distilled under argon from molten sodium. Bis-trimethylphosphinetitanocene, $Cp_2Ti(PMe_3)_2$, was prepared from titanocene dichloride (obtained from Boulder Scientific, Boulder, CO) by the procedure of Binger, et. al.[87] and was stored in a dry box under argon. *t*-$BuMe_2SiCN$ was prepared from *t*-$BuMe_2SiCl$ and KCN in the presence of 18-Crown-6.[88] Et_3SiCN was prepared by the procedure of Becu[89] (Me_3SiCN, Et_3SiCl, trace KF, then removal of Me_3SiCl by distillation). The enynes 3-Allyloxy-1-phenyl-1-propyne, 3-(2-methyl-2-propenyloxy)-1-phenyl-1-propyne, and 3-allyloxy-1-phenyl-1-butyne (Table 7, entries 1, 9 and 10) were prepared by the condensation of allyl bromide with the appropriate propargyl alcohol (NaH, dry THF).[90] 1-Phenyl-6-hepten-1-yne[91] (Table 7, entry 4) was synthesized by the reaction of lithium phenylacetylide (prepared *in situ* from *n*-BuLi and phenylacetylene in THF at 0 °C) and 5-bromo-1-pentene in the presence of 2 equiv of DMPU (reflux, 3 h). Diethyl 7-octen-2-yne-5,5-carboxylate[76] (Table 7, entry 7) was prepared by the alkylation of diethyl allylmalonate with 1-methylpropargyl mesylate (NaI, K_2CO_3, acetone, reflux, 4 days). Syntheses of previously unreported enyne substrates are described below. All other reagents were available from commercial sources and were used without further purification, unless noted otherwise.

Preparative 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/or ^1H NMR analysis. All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. Previously unreported compounds were also characterized by high resolution mass spectroscopy. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian

Unity 300, or a Bruker AC 250 Fourier transform spectrometer. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; 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 the central line of the 77.0 ppm triplet for deuterochloroform. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer. High resolution mass spectra were recorded on a Finnegan MAT System 8200. Gas chromatography (GC) analyses 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. Melting points were measured on a Haake Buchler Melting Point Apparatus and are uncorrected.

Preparation of Enyne Starting Materials

N-Allyl-N-(3-phenylpropynyl)aniline (Table 7, entry 2). Allylaniline (4.1 mL, 30 mmol) and THF (100 mL) were added to a dry Schlenk flask under argon. The solution was cooled to -78 °C (dry ice/acetone bath) and *n*-BuLi (12 mL, 2.5 M in hexanes, 31 mmol) was added dropwise. 1-Phenylpropargyl bromide (6.0 g, 30 mmol) was then added, and the reaction mixture was allowed to warm to r.t. overnight. The next day, the mixture was added to a separatory funnel with 150 mL each of 1 N HCl and ether. The organic layer was separated and washed with 3x50 mL of 1 N HCl and 50 mL of brine. After drying the solution over $MgSO_4$, flash chromatography (CH_2Cl_2 : hexane = 1 : 99) provided 4.3 g (58% yield) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3-7.4 (m, 2 H), 7.2-7.3 (m, 5 H), 6.91 (d, J = 9 Hz, 2 H), 6.78 (t, J = 9 Hz, 1 H), 5.8-6.0 (m, 1 H), 5.30 (dd, J = 2 Hz, J = 17 Hz, 1 H), 5.20 (dd, J = 2 Hz, J = 10 Hz, 1 H), 4.23 (s, 2 H), 4.03 (d, J = 5.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 134.2, 131.7, 129.1, 128.2, 128.1, 123.1, 118.0, 116.7, 114.3, 85.6, 83.9, 53.9, 40.6; IR (neat): 3297, 3060,

3032, 2979, 2912, 2245, 1642, 1598, 1575, 1503, 1490, 1442, 1417, 1378, 1346, 1287, 1255, 1229, 1192, 1173, 1126, 1255, 1229, 1192, 1173, 990, 911, 755, 733, 691 cm^{-1}; Exact mass calculated for $C_{18}H_{17}N$: 247.1361. Found: 247.1363.

***tert*-Butyl N-allyl-N-(2-butynyl)carboxylate (Table 7, entry 3).** 1-Methylpropargyl mesylate (7.0 g, 47 mmol, freshly prepared from 2-butyn-1-ol and methanesulfonyl chloride) was added neat to allylamine (17.6 mL, 235 mmol) with stirring at 0 °C (ice bath). The bath was allowed to warm to r.t., at which point GC analysis showed the complete disappearance of the mesylate. The reaction mixture was added to 150 mL of ether, and the white precipitate which formed was filtered away. Distillation (130 °C, 760 mm Hg) provided the desired N-allyl-N-(2-butynyl)amine. This material (2.0 g, 18 mmol) was then added to ether (50 mL) in a 250 mL Schlenk flask under argon. Pyridine (1.54 mL, 19 mmol) was added, and the solution was cooled to 0 °C (ice bath). Di-*t*-butylcarbonate (4.37 mL, 19 mmol) was then added dropwise, and the reaction mixture was allowed to warm to r.t. The reaction mixture was then diluted with ether (75 mL) and washed with 3x50 mL of 1 N NaOH. The organic layer was dried over $MgSO_4$ and purified by vacuum distillation (47 °C, 0.02 mm Hg) to afford the desired product as a clear oil: ^1H NMR (300 MHz, $CDCl_3$): δ 5.7-5.85 (m, 1 H), 5.17 (d, J = 7.4 Hz, 1 H), 5.14 (d, J = 11 Hz, 1 H), 3.97 (s, 2 H), 3.92 (d, J = 5.7 Hz, 2 H), 1.81 (t, J = 2.3 Hz, 3 H), 1.46 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 133.5, 116.6, 79.8, 78.9, 74.6, 48.2, 35.5, 28.2, 3.3; IR (neat): 3082, 2977, 2922, 2226, 1699, 1455, 1406, 1366, 1246, 1173, 1146, 924, 872, 769 cm^{-1}; Exact mass calculated for $C_{12}H_{19}NO_2$: 209.1416. Found: 209.1414.

Di-*tert*-butyl 2-pentyne-5,5-dicarboxylate. Sodium hydride (3.71 g, 155 mmol) was slurried in dry *tert*-butyl alcohol (100 mL) and cooled to 0 °C under an atmosphere of argon. After 15 min, di-*tert*-butylmalonate (46.1 mL, 206 mmol) was added dropwise.

The mixture was then warmed to room temperature, and the mesylate of 2-butyn-1-ol (15.3 g, 103 mmol), freshly prepared by the reaction of MsCl and 2-butyn-1-ol in ether with triethylamine, was added. Additional *tert*-butyl alcohol (50 mL) was added and the mixture was heated to 65 °C. After 1 h, the mixture was cooled to room temperature and added to a separatory funnel with 100 mL H_2O. The aqueous layer was then separated and extracted with 3x100 mL of ether. The combined organic layers were dried over K_2CO_3, filtered, and concentrated under reduced pressure. A trace amount of magnesium oxide was added to prevent decomposition. Vacuum distillation (100 °C, 0.15 mm Hg) in base-washed glassware afforded the desired product (18.89 g, 70.5 mmol, 69% yield), which was used immediately in the following two preparations:

Di-*tert*-butyl 7-octen-2-yne-5,5-dicarboxylate[92] (Table 7, entry 5). Sodium hydride (0.85 g, 35.3 mmol) was placed under an atmosphere of argon and slurried in toluene (120 mL). Di-*tert*-butyl 2-pentyne-5,5-dicarboxylate (6.3 g, 23.5 mmol) and additional toluene (20 mL) were added, and the mixture was heated to 85 °C. After 2.5 h, the mixture was cooled to room temperature. Allyl bromide (2.45 mL, 28.2 mmol) in toluene (20 mL) was added, and the mixture was again heated to 85 °C. The mixture was stirred overnight, and then cooled to r.t. *p*-Toluenesulfonic acid (2.03 g, 11.8 mmol) was added slowly, and the reaction mixture was stirred for 5 min. The mixture was filtered, concentrated under reduced pressure, and vacuum distilled (108 °C, 0.15 mm Hg) in base-washed glassware, yielding the desired product (2.66 g, 8.6 mmol, 38% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.5-5.7 (m, 1 H), 5.0-5.2 (m, 2 H), 2.66 (d, J = 7.4 Hz, 2 H), 2.59 (q, J = 2.6 Hz, 2 H), 1.72 (t, J = 2.6 Hz, 3 H), 1.42 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 132.5, 119.0, 81.4, 78.3, 73.9, 57.6, 36.3, 27.8, 22.7, 3.4; IR (neat): 3079, 3004, 2931, 2250, 1731, 1642, 1477, 1456, 1437, 1393, 1369, 1298, 1250, 1227, 1153, 1068, 993, 921, 847, 747 cm^{-1}; Exact mass calculated for $C_{14}H_{20}O_4$ [M-C_4H_8]$^+$: 252.1361. Found: 252.1360.

Di-*tert*-butyl-8-nonen-2-yne-5,5-dicarboxylate[92] (Table 7, entry 6). Sodium hydride (0.85 g, 35.3 mmol) was placed under an atmosphere of argon and slurried in toluene (120 mL). Di-*tert*-butyl 2-pentyne-5,5-dicarboxylate (6.3 g, 23.5 mmol) and additional toluene (20 mL) were added and the mixture was heated to 80 °C. After 2.5 h, the mixture was cooled to r.t. 4-Bromo-1-butene (2.45 mL, 28.2 mmol) in toluene (20 mL) was added, and the mixture was again heated to 80 °C. After 1 day, sodium iodide (0.70 g, 4.7 mmol) was added. After 2 additional days, the reaction was cooled to r.t., *p*-toluenesulfonic acid (2.03 g, 11.8 mmol) was added slowly, and the reaction mixture was stirred for 5 min. The mixture was filtered, concentrated under reduced pressure and vacuum distilled (115 °C, 0.15 mm Hg) in base-washed glassware. The crude product obtained was then purified by flash chromatography (92 : 8 hexane : diethyl ether), yielding the desired product (2.28 g, 7.07 mmol, 30% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.7-5.9 (m, 1 H), 4.9-5.1 (m, 2 H), 2.62 (q, J = 2.4 Hz, 2 H), 1.85-2.05 (m, 4 H), 1.70 (t, J = 2.4 Hz, 3 H), 1.41 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 138.0, 114.7, 81.3, 78.2, 73.8, 57.7, 30.9, 28.3, 27.8, 22.9, 3.1; IR (neat): 3078, 2977, 2933, 2275, 1729, 1642, 1477, 1451, 1393, 1359, 1280, 1245, 1216, 1160, 912, 849 cm^{-1}; Exact mass calculated for $C_{15}H_{22}O_4$ $[M-C_4H_8]^+$: 266.1518. Found: 266.1520.

Diethyl 1-(dimethylsilyl)-6-hepten-1-yne-5,5-dicarboxylate (Table 7, entry 8). To a solution of *i*-Pr_2NH (12.9 mL, 92.5 mmol) in THF (75 mL) was added *n*-BuLi (35.6 mL, 2.6 M in hexanes, 92.5 mmol) at 0 °C (ice bath) under argon. The solution was transferred by cannula into a solution of diethyl allylmalonate (13.6 mL, 69 mmol) in THF (150 mL) at -78 °C (dry ice/acetone bath) with stirring. After the addition was complete, propargyl bromide (10.7 mL, 80 wt % wt in toluene, 96.2 mmol) was added, the cold bath was removed, and the reaction mixture was allowed to warm to r.t. overnight. The next day, the reaction was quenched by slow addition of sat. aq. NH_4Cl

(~50 mL) and the contents of the reaction flask were added to a separatory funnel with 150 mL each of ether and H_2O. The organic layer was separated and washed with 2x100 mL of 1 N HCl and 100 mL of brine, and then dried over $MgSO_4$. Vacuum distillation afforded 10.7 g (65% yield) of diethyl 6-hepten-1-yne-4,4-dicarboxylate. To a solution of this material (9.25 g, 39 mmol) in THF (70 mL) at -78 °C (dry ice/acetone bath) was added a freshly prepared solution (see above) of lithium diisopropylamide (46 mmol in 70 mL of THF) by cannula. When the addition was complete, the reaction mixture was stirred for 10 min. Chlorodimethylsilane (5.1 mL, 46 mmol) was then added and the mixture was stirred at -78 °C for 1 h. The reaction was then quenched by slow addition of 40 mL of sat. aq. NH_4Cl at low temperature. Upon warming to r.t., the mixture was added to 100 mL each of ether and H_2O. The aqueous layer was separated and extracted with 25 mL of ether, and the combined organic layers were washed with 2x50 mL of sat. aq. $CuSO_4$ and 50 mL of brine. The solution was dried over $MgSO_4$ and purified by vacuum distillation (87-90 °C, 0.02 mm Hg) followed by flash chromatography[93] (ether : hexane = 5 : 95) to afford the desired product as a clear oil: ^1H NMR (300 MHz, $CDCl_3$): δ 5.5-5.7 (m, 1 H), 5.17 (dd, J = 2.0 Hz, J = 20 Hz, 1 H), 5.13 (dd, J = 2.0 Hz, J = 9.3 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 4 H), 4.08 (m, 1 H), 2.83 (s, 2 H), 2.80 (d, J = 7.5 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 6 H), 0.20 (d, J = 3.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 131.8, 119.6, 102.8, 85.0, 61.5, 56.7, 36.4, 23.9, 14.0, -3.0; IR (neat): 3080, 2981, 2181, 2137, 1736, 1444, 1367, 1322, 1286, 1251, 1215, 1190, 1145, 1096, 1032, 885, 841, 772, 742 cm^{-1}; Exact mass calculated for $C_{14}H_{21}O_4Si$ $[M - CH_3]^+$: 281.1209. Found: 281.1208.

5-(Triisopropylsilyloxy)-1-undecen-6-yne (Table 7, entry 11). To a 50 mL two-necked flask under nitrogen, added imidazole (2.7 g, 40 mmol) and DMF (20 mL). After the imidazole had dissolved, undec-1-en-6-yn-5-ol (3.3 g, 20 mmol, made by the addition of 1-hexynyllithium, prepared *in situ* from *n*-BuLi and 1-hexyne in THF at 0 °C, to 4-penten-1-al, generated by the Swern oxidation of 4-penten-1-ol.[94]) was added to the

solution. Triisopropylsilyl chloride (4.2 mL, 20 mmol) was then added dropwise, and the mixture was stirred at r.t. After 4 h, the reaction mixture was poured into a separatory funnel with 75 mL each of ether and sat. aq. $CuSO_4$. The organic layer was separated and washed with 30 mL each of sat. aq. $CuSO_4$, H_2O, and brine. The solution was then dried over $MgSO_4$ and purified by vacuum distillation to afford 1.9 g (30 % yield) of a clear oil: ^1H NMR (300 MHz, $CDCl_3$): δ 5.8-5.9 (m, 1 H), 5.03 (dd, J = 2.0 Hz, J = 18 Hz, 1 H), 4.96 (dd, J = 2.0 Hz, J = 10 Hz, 1 H), 4.4-4.5 (m, 1 H), 2.15-2.3 (m, 4 H), 1.75 (dd, J = 7.9 Hz, J = 14 Hz, 2 H), 1.3-1.5 (m, 4 H), 1.0-1.1 (m, 21 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 114.5, 84.6, 81.7, 62.7, 38.5, 30.8, 29.5, 22.0, 18.5, 18.2 (two overlapping signals), 13.7, 12.4; IR (neat): 3078, 2942, 2866, 2262, 1641, 1464, 1340, 1248, 1092, 1014, 996, 912, 883, 681 cm^{-1}; Exact mass calculated for $C_{17}H_{31}OSi$ $[M - C_3H_7]^+$: 279.2144. Found: 279.2143.

6-(Triisopropylsilyloxy)-1-dodecen-7-yne (Table 7, entry 12). To a 100 mL three-necked flask under argon, added imidazole (3.95 g, 58 mmol) and DMF (30 mL). After the imidazole had dissolved, dodec-1-en-7-yn-6-ol (5.23 g, 29 mmol, made by the addition of 1-hexynyllithium (prepared *in situ* from *n*-BuLi and 1-hexyne in THF at 0 °C) to 5-hexen-1-al, generated by the Swern oxidation of 5-hexen-1-ol.[94]) was added to the solution. The reaction vessel was placed in a r.t. water bath, and triisopropylsilyl triflate (8.6 mL, 32 mmol) was then added dropwise. The mixture was stirred at r.t. for 4 h, then diluted with 75 mL of ether and washed with 2x75 mL of sat. aq. $CuSO_4$. The aqueous washings were then extracted with 2x50 mL of ether, and the combined organic layers were washed with 2x50 mL each of H_2O and brine. The solution was dried over $MgSO_4$, and purified by vacuum distillation (155 °C, 0.02 mm Hg) to afford 5.69 g (58 % yield) of a clear oil: ^1H NMR (300 MHz, $CDCl_3$): δ 5.7-5.9 (m, 1 H), 4.9-5.05 (m, 2 H), 4.4-4.5 (m, 1 H), 2.18 (td, J = 6.9 Hz, J = 1.8 Hz, 2 H), 2.08 (q, J = 6.9 Hz, 2 H), 1.3-1.7 (m, 8 H), 1.0-1.2 (m, 21 H), 0.90 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7,

114.3, 84.4, 81.9, 63.1, 38.7, 33.6, 30.8, 24.5, 22.0, 18.5, 18.2, 18.1, 13.7, 12.4; IR (nujol): 3077, 2942, 2866, 2250, 1641, 1464, 1382, 1339, 1248, 1149, 1093, 1066, 1014, 996, 910, 883, 681 cm^{-1}; Exact mass calculated for $C_{18}H_{33}OSi$ [M - C_3H_7]$^+$: 293.2301. Found: 293.2299.

3-Benzyloxy-1-undecen-6-yne (Table 7, entry 13). To a slurry of NaH (1.72 g, 72 mmol) in THF (100 mL) in a 500 mL round-bottom Schlenk flask under argon was added undec-1-en-6-yn-3-ol[95] (10.4 g, 63 mmol) and benzyl bromide (8.55 mL, 72 mmol). The reaction mixture was heated to reflux for 5 h, then the reaction was quenched by addition of ~40 mL of NH_4Cl. The mixture was then added to a separatory funnel with 80 mL each of H_2O and ether. The aqueous layer was separated and extracted with 2x75 mL of ether. The combined organic extracts were then washed with 2x80 mL of brine and dried over $MgSO_4$. Purification by vacuum distillation (150 °C, 0.02 mm Hg) afforded 7.2 g (45 % yield) of a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2-7.4 (m, 5 H), 5.6-5.8 (m, 1 H), 5.26 (dd, J = 1.9 Hz, J = 8.0 Hz, 1 H), 5.21 (s, 1 H), 4.59 (d, J = 12 Hz, 1 H), 4.36 (d, J = 12 Hz, 1 H), 3.89 (q, J = 5.5 Hz, 1 H), 2.2-2.3 (m, 2 H), 2.0-2.2 (m, 2 H), 1.75-1.9 (m, 1 H), 1.6-1.75 (m, 1 H), 1.3-1.5 (m, 4 H), 0.89 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.5, 128.2, 127.7, 127.3, 117.2, 80.5, 79.4, 79.2, 70.3, 34.9, 31.2, 21.8, 18.3, 14.9, 13.5; IR (neat): 3065, 3030, 2956, 2930, 2861, 1642, 1496, 1454, 1432, 1329, 1098, 1071, 1028, 993, 927, 735, 697 cm^{-1}; Exact mass calculated for $C_{18}H_{23}O$ [M - H]$^+$: 255.1749. Found: 255.1750.

Conversion of Enynes to Bicyclic Cyclopentenones

General Procedure A. $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) and the enyne (2.0 mmol) were added to a dry Schlenk tube in a dry box under argon. The mixture was stirred for 5 min, and the tube was fitted with an addition funnel. The funnel was charged

with a solution of Me_3SiCN (293 μL, 2.2 mmol) in benzene (2 mL), and this was added dropwise to the reaction mixture over a period of 4-8 h. After the addition of Me_3SiCN was complete, the tube was removed from the dry box (without exposing the contents to the atmosphere) and attached to a vacuum/argon manifold. The benzene was then removed *in vacuo*, the residue placed under an atmosphere of argon, and THF (10 mL) and 1 N HCl (4 mL) were added. The mixture was stirred vigorously for 12-16 h, then poured into a separatory funnel with 50 mL each of ether and H_2O. The aqueous layer was separated and extracted with 2x30 mL of ether, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated using a rotary evaporator to afford the crude product.

General Procedure B. $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) was added to a dry, sealable Schlenk tube in a dry box under argon. Benzene (1 mL) and the enyne (2.0 mmol) were then added with stirring. After 2-3 min, a solution of *t*-$BuMe_2SiCN$ (326 mg, 2.3 mmol) in benzene (1 mL) was added. The tube was then sealed, removed from the dry box, and attached to a vacuum/argon maniforld. The reaction vessel was then immersed in an oil bath heated to 45 °C for 20-24 h, after which time the starting material had been completely converted to the corresponding bicyclic iminocyclopentene (^1H NMR analysis). The vessel was removed from the oil bath and the reaction mixture was transferred by cannula to a 250 mL Schlenk flask under argon. The benzene was removed *in vacuo*, and THF (30 mL) was added. The solution was cooled in an ice bath, and 30 mL of a 1:1 mixture of 1.0 M acetic acid and 1.0 M sodium acetate (the pH of this buffered solution was ca. 5) was added dropwise over a period of 5 min with vigorous stirring. After 2-4 h, hydrolysis to the cyclopentenone was judged to be complete,[96] and the mixture was allowed to separate into two layers. The aqueous layer was extracted with 3x30 mL of ether, and the combined organic layers were washed with 30 mL each of 1 N NH_4F, H_2O, and brine, and then dried over $MgSO_4$. Concentration using a rotary

evaporator afford the crude product.

General Procedure C. To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) under argon was added benzene or toluene (2 mL) and the enyne (2.0 mmol). Et_3SiCN (390 μL, 2.3 mmol) was then added, the tube was sealed, and the reaction vessel was immersed in an oil bath heated to 45 °C. After stirring for 16-24 h, the starting material had been completely converted to the corresponding bicyclic iminocyclopentene (^1H NMR analysis). The vessel was removed from the oil bath and the reaction mixture was transferred by cannula to a 250 mL Schlenk flask under argon. The solvent was then removed *in vacuo*, and THF (40 mL) was added, followed by dropwise addition of 3 mL of sat. aq. $CuSO_4$. After vigorous stirring for 3-6 h, hydrolysis to the cyclopentenone was judged to be complete,[96] and the reaction mixture was poured into a separatory funnel with 50 mL each of 0.5 N HCl and ether. The aqueous layer was separated and extracted with two additional 50 mL portions of ether. The combined organic layers were then washed with 50 mL portions of 0.5 N HCl and brine, and then dried over $MgSO_4$. Concentration using a rotary evaporator afford the crude product.

2-Phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one[58] (Table 7, entry 1). Procedure A was used to convert 3-allyloxy-1-phenyl-1-propyne[58] (344 μL, 2.0 mmol) to the desired product. Purification by Kugelrohr vacuum distillation afforded 319 mg (80% yield) of pure product as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$): δ 7.25-7.55 (m, 5 H), 4.95 (d, J = 16 Hz, 1 H), 4.44 (d, J = 16 Hz, 1 H), 4.38 (t, J = 7.3 Hz, 1 H), 3.2-3.4 (m, 2 H), 2.85 (dd, J = 6.1 Hz, J = 18 Hz, 1 H), 2.35 (dd, J = 2.8 Hz, J = 18 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 177.3, 134.2, 130.4, 128.3 (two overlapping signals), 127.7, 71.0, 66.0, 43.0, 40.0; IR (neat): 3058, 2976, 2853, 1744, 1707, 1497, 1446, 1408, 1356, 1301, 1165, 1120, 1027, 908, 890, 767, 732, 697 cm^{-1}.

2,7-Diphenyl-7-azabicyclo[3.3.0]oct-1-en-3-one (Table 7, entry 2). Procedure A was used to convert N-phenyl-N-(3-phenyl-2-propynyl)-N-allylaniline (494 mg, 2.0 mmol) to the desired product. Purification by recrystallization from ethyl acetate afforded 240 mg (44% yield) of pure product as yellow crystals: m. p.: 204-206 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56 (d, J = 7.0 Hz, 2 H), 7.2-7.45 (m, 5 H), 6.74 (t, J = 7.3 Hz, 1 H), 6.63 (d, J = 8.1 Hz, 2 H), 4.62 (d, J = 16 Hz, 1 H), 4.07 (d, J = 16 Hz, 1 H), 3.95 (t, J = 8.5 Hz, 1 H), 3.3-3.5 (m, 1 H), 2.89 (dd, J = 6.5 Hz, J = 18 Hz, 1 H), 2.76 (t, J = 9.3 Hz, 1 H), 2.44 (dd, J = 3.6 Hz, J = 18 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 206.3, 174.9, 163.6, 147.2, 135.2, 130.7, 129.3, 128.5, 128.2, 117.1, 112.0, 51.8, 49.4, 41.3, 31.0; IR (nujol): 1688, 1645, 1598, 1506, 1468, 1444, 1379, 1358, 1158, 994, 905, 752, 699 cm^{-1}; Exact mass calculated for $C_{19}H_{17}NO$: 275.1310. Found: 275.1308. Flash chromatography (ethyl acetate : hexane = 15 : 85) of the residue obtained by removal of solvent from the mother liquor afforded 63 mg (13%) of the starting enyne.

***t*-Butyl 2-methyl-7-azabicyclo[3.3.0]oct-1-en-3-one-7-carboxylate (Table 7, entry 3).** Procedure C was followed to convert *t*-butyl N-allyl-N-(2-butynyl)carboxylate (416 mg, 2.0 mmol) to the corresponding bicyclic iminocyclopentene. After the $CuSO_4$-mediated hydrolysis was judged to be complete (6 h), the reaction mixture was poured into a separatory funnel with 50 mL each of ether and H_2O. The aqueous layer was separated and extracted with 50 mL of ether and 2x30 mL of ethyl acetate. The combined organic extracts were then washed with brine and dried over $MgSO_4$ to afford, after purification by flash chromatography (ether : hexane = 7 : 3), 203 mg (43% yield) of the product as a light yellow solid: m. p.: 113-115 °C; NMR spectroscopy showed the product to be a slowly equilibrating mixture of two rotamers (R1 and R2) as a result of restricted rotation about the carbon-nitrogen amide bond: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (s, 2 H, R1), 4.08 (s, 2 H, R2), 3.98 (t, J = 9.4 Hz, 1 H, R1), 3.90 (t, J = 9.4 Hz, 1 H, R2), 3.07 (s, 1 H, R1 + R2), 2.72 (t, J = 8.1 Hz, 1 H, R1), 2.69 (t, J = 8.1 Hz, 1 H, R2), 2.61 (t, J = 6.5 Hz, 1

H, R1), 2.55 (t, J = 6.5 Hz, 1 H, R2), 2.09 (s, 1 H, R1), 2.03 (s, 1 H, R2), 1.68 (s, 3 H, R1), 1.67 (s, 3 H, R2), 1.41 (s, 9 H, R1), 1.40 (s, 9 H, R2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0 (R1+R2), 172.4 (R1), 171.9 (R2), 153.8 (R1), 153.6 (R2), 132.8 (R1), 132.7 (R2), 79.4 (R1+R2), 50.5 (R1), 49.8 (R2), 45.1 (R1), 44.7 (R2), 41.1 (R1), 40.4 (R2), 39.1 (R1), 39.0 (R2), 27.9 (R1+R2), 8.2 (R1+R2); IR (nujol): 1707, 1683, 1308, 1291, 1166, 1109, 1049, 967, 870, 771, 722 cm^{-1}; Exact mass calculated for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1363.

2-Phenylbicyclo[3.3.0]oct-1-en-3-one[91] (Table 7, entry 4). Both procedure A and procedure B were used to convert 1-phenyl-6-hepten-1-yne[91] (340 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether : hexane = 3 : 7) afforded 218 mg (55% yield) of a pale yellow powder using procedure A and 262 mg (66% yield) using procedure B: m. p.: 62-63 °C (no lit. value reported); ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 7.0 Hz, 2 H), 7.15-7.35 (m, 3 H), 2.65-2.9 (m, 3 H), 2.45-2.6 (m, 1 H), 2.05-2.2 (m, 2 H), 1.95-2.05 (m, 2 H), 1.04 (quint, J = 9.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0, 184.8, 133.7, 131.2, 127.6, 127.5, 127.0, 44.0, 42.3, 30.3, 26.7, 25.3; IR (nujol): 1710, 1690, 1625, 1314, 1297, 1132, 926, 763, 695 cm^{-1}.

Di-*t*-butyl 2-methylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (Table 7, entry 5). Procedure B was used to convert di-*t*-butyl 7-octen-2-yne-4,4,-dicarboxylate (616 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether : hexane = 1 : 4) afforded 474 mg (70% yield) of a white solid: m. p.: 67-69 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 2 H), 2.8-2.9 (m, 1 H), 2.45-2.6 (m, 2 H), 1.96 (dd, J = 3.0 Hz, J = 17 Hz, 1 H), 1.62 (t, J = 1.1 Hz, 3 H), 1.46 (t, J = 12 Hz, 1 H), 1.39 (s, 9 H), 1.37 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 178.4, 170.7, 170.1, 132.6, 81.8, 81.7, 62.2, 42.5, 41.3, 38.9, 33.7, 27.7 (two overlapping signals), 8.4; IR (nujol): 1725, 1672, 1457, 1369, 1284, 1256, 1169, 1141, 1062, 1029, 845 cm^{-1}; Exact mass calculated for $C_{15}H_{20}O_5$ [M -

$C_4H_8]^+$: 294.1467. Found: 294.1465.

Di-*t*-butyl 2-methylbicyclo[3.4.0]non-1-en-3-one-8,8-dicarboxylate (Table 7, entry 6). Procedure B was used to convert di-*t*-butyl 8-nonen-2-yne-4,4-dicarboxylate (644 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether : hexane = 3 : 7) afforded 497 mg (71% yield) of a clear viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (dd, J = 2.2 Hz, J = 14 Hz, 1 H), 2.35-2.6 (m, 4 H), 2.05-2.15 (m, 1 H), 1.8-2.0 (m, 2 H), 1.76 (s, 3 H), 1.48 (s, 9 H), 1.41 (s, 9 H), 1.2-1.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 170.7, 170.5, 168.8, 135.4, 82.0, 81.4, 57.2, 40.8, 39.2, 33.1, 30.9, 30.5, 27.8 (two overlapping signals), 7.8; IR (neat): 3056, 2976, 2931, 2862, 1709, 1656, 1496, 1445, 1295, 1270, 1132, 1046, 988, 904, 834, 767, 711, 696, 606 cm^{-1}; Exact mass calculated for $C_{16}H_{22}O_5$ $[M-C_4H_8]^+$: 280.1311. Found: 280.1312.

Diethyl 2-methylbicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate[76] (Table 7, entry 7) Procedure B was used to convert diethyl 7-octen-2-yne-4,4-dicarboxylate[76] (504 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether : hexane = 2 : 3) afforded 366 mg (65% yield) of a white waxy solid. A modification of procedure B where Et_3SiCN (390 μL, 2.3 mmol) was used in place of *t*-$BuMe_2SiCN$ provided, after purification, 400 mg (71% yield) of the same material: m. p.: 33-36 °C (no lit. value reported); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (q, J = 7.1 Hz, 2 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.24 (d, J = 12 Hz, 1 H), 3.20 (d, J = 12 Hz, 1 H), 2.99 (m, 1 H), 2.79 (dd, J = 7.2 Hz, J = 12 Hz, 1 H), 2.65 (dd, J = 6.5 Hz, J = 18 Hz, 1 H), 2.10 (dd, J = 3.5 Hz, J = 18 Hz, 1 H), 1.72 (t, J = 1.0 Hz, 3 H), 1.66 (t, J = 12 Hz, 1 H), 1.30 (t, J = 6.8 Hz, 3 H), 1.27 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 178.0, 171.8, 171.2, 133.1, 62.3, 62.1, 61.2, 42.9, 41.6, 39.4, 34.2, 14.2 (two overlapping signals), 8.7; IR (nujol): 1736, 1675, 1460, 1424, 1384, 1256, 1177, 1084, 1063, 1023 cm^{-1}.

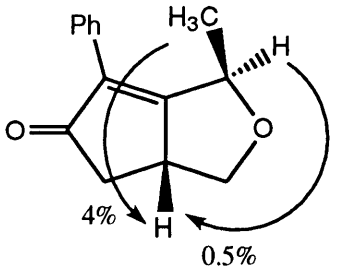
Diethyl bicyclo[3.3.0]oct-1-en-3-one-7,7-dicarboxylate (Table 7, entry 8). To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) under argon was added benzene (2 mL) and diethyl 1-(dimethylsilyl)-6-hepten-1-yne-4,4-dicarboxylate (592 mg, 2.0 mmol). Et_3SiCN (390 μL, 2.3 mmol) was then added, the tube was sealed, and the reaction mixture was stirred at r.t. for 27 h. The solution was transferred by cannula to a 250 mL Schlenk flask under argon, and the solvent was removed *in vacuo*. THF (15 mL) and CH_2Cl_2 (15 mL) were then added, and the reaction vessel was cooled to 0 °C (ice bath). Trifluoroacetic acid (5 mL) and H_2O (0.5 mL) were then added slowly, and the reaction mixture was stirred vigorously as the ice bath warmed to r.t. After 16 h, 60 mL of sat. aq. $NaHCO_3$ was added SLOWLY to avoid bubbling over. When the bubbling ceased, the mixture was added to a separatory funnel with 80 mL each of ether and H_2O. The aqueous layer was separated and extracted with 30 mL portions of ether and ethyl acetate. The combined organic layers were then washed with brine and dried over $MgSO_4$, followed by concentration using a rotary evaporator. Purification by flash chromatography (ether : hexane = 1 : 1, then 100% ether) afforded 280 mg (53% yield) of the desired cyclopentenone and 125 mg (22% yield) of the corresponding β-hydroxy ketone **62**: **Cyclopentenone:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 1 H), 4.26 (q, J = 6.9 Hz, 2 H), 4.22 (q, J = 6.8 Hz, 2 H), 3.36 (d, J = 19 Hz, 1 H), 3.26 (d, J = 19 Hz, 1 H), 3.12 (m, 1 H), 2.81 (dd, J = 7.8 Hz, J = 13 Hz, 1 H), 2.64 (dd, J = 6.4 Hz, J = 18 Hz, 1 H), 2.14 (dd, J = 3.1 Hz, J = 18 Hz, 1 H), 1.75 (t, J = 13 Hz, 1 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 185.3, 171.1, 170.4, 125.3, 62.0, 61.9, 60.7, 44.9, 42.0, 38.8, 35.1, 14.0 (two overlapping signals); IR (neat): 2882, 2938, 1733, 1634, 1464, 1447, 1413, 1390, 1367, 1254, 1178, 1096, 1064, 1039, 1017, 901, 860, 821 cm^{-1}; Exact mass calculated for $C_{14}H_{18}O_5$: 266.1154. Found: 266.1155; **β-Hydroxy ketone:** ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.1-4.3 (m, 4 H), 3.28 (s, 1 H), 2.6-2.8 (m, 4 H), 2.56 (s, 2 H), 2.36 (d, J = 15 Hz, 1 H), 2.0-2.2 (m, 2 H), 1.2-1.3 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.7, 173.2, 171.1, 85.4,

62.2, 61.8, 59.9, 51.3, 48.0, 46.8, 44.0, 39.5, 13.9 (two overlapping signals); IR (neat): 3468 (br), 2982, 2940, 1740, 1465, 1446, 1392, 1368, 1258, 1187, 1097, 1044, 916, 860, 733 cm^{-1}; Exact mass calculated for $C_{14}H_{20}O_6$: 284.1260 Found: 284.1258.

2-Phenyl-5-methyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (Table 7, entry 9). To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (132 mg, 0.4 mmol, 20 mol %) under argon was added benzene (2 mL) and 3-(2-methyl-2-propenyloxy)-1-phenyl-1-propyne[90] (372 mg, 2.0 mmol). Et_3SiCN (407 μL, 2.4 mmol) was then added, the tube was sealed, and the reaction vessel was immersed in an oil bath heated to 45 °C. After stirring for 24 h, the vessel was removed from the oil bath and the reaction mixture was transferred by cannula to a 250 mL Schlenk flask under argon. The solvent was then removed *in vacuo* and THF (40 mL) was added, followed by dropwise addition of 5 mL of sat. aq. $CuSO_4$. After vigorous stirring for 28 h, hydrolysis was judged to be complete,[96] and the reaction was worked up according to Procedure C. Purification by flash chromatography (ether : hexane = 3 : 7) afforded 253 mg (59% yield) of a viscous yellow oil: ^1H NMR (300 MHz, $CDCl_3$): δ 7.3-7.6 (m, 5 H), 4.99 (d, J = 16 Hz, 1 H), 4.61 (d, J = 16 Hz, 1 H), 4.04 (d, J = 7.9 Hz, 1 H), 3.43 (d, J = 7.9 Hz, 1 H), 2.61 (d, J = 15 Hz, 1 H), 2.54 (d, J = 15 Hz, 1 H), 1.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 180.5, 133.1, 130.5, 128.6, 128.5, 128.1, 76.5, 65.3, 48.7, 47.8, 24.7; IR (nujol): 3056, 2967, 2852, 1712, 1654, 1496, 1446, 1345, 1295, 1151, 1072, 1025, 918, 896, 766, 697, 597 cm^{-1}; Exact mass calculated for $C_{14}H_{14}O_2$: 214.0994. Found: 214.0996.

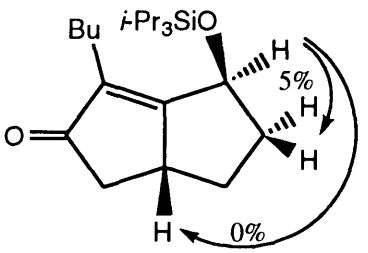
2-Phenyl-8-methyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (Table 7, entry 10). Procedure B was used to convert 3-allyloxy-1-phenyl-1-butyne (372 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether : hexane = 3 : 7) afforded 305 mg (71% yield) of a pale yellow viscous oil as a 5:1 mixture of diastereomers: **Major isomer**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J = 7.0 Hz, 2 H), 7.3-7.45 (m, 3 H), 4.85

(q, J = 6.5 Hz, 1 H), 4.35 (t, J = 7.8 Hz, 1 H), 3.35-3.45 (m, 1 H), 3.25 (dd, J = 7.8 Hz, J = 11 Hz, 1 H), 2.79 (dd, J = 6.4 Hz, J = 18 Hz, 1 H), 2.28 (dd, J = 3.5, J = 18 Hz, 1 H), 1.56 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 179.5, 134.1, 130.2, 128.5, 127.8, 127.7, 71.7, 70.6, 41.2, 39.0, 20.7. **Minor Isomer**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 2 H), 7.3-7.45 (m, 3 H), 5.23 (q, 1 H), 4.27 (s, 1 H), 3.35-3.45 (m, 1 H), 3.25 (dd, 1 H), 2.78 (dd, 1 H), 2.34 (dd, 1 H), 1.14 (d, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 181.6, 135.3, 129.5, 127.9, 127.8, 127.6, 72.2, 68.9, 44.5, 39.5, 16.7; IR (neat): 2977, 2933, 2869, 1727, 1659, 1456, 1393, 1369, 1287, 1257, 1166, 1139, 1072, 847, 734 cm^{-1}; Exact mass calculated for $C_{14}H_{14}O_2$: 214.0994. Found: 214.0995. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the methyl group at δ 1.56 gave a 4% NOE of the C-5 hydrogen at δ 3.4. Irradiation of the C-8 hydrogen at δ 4.85 gave about 0.5% enhancement of the same hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:



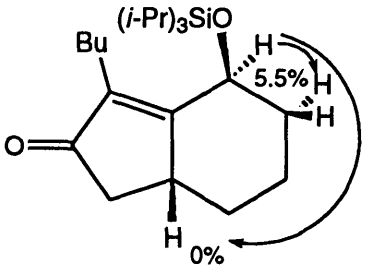
2-Butyl-8-(triisopropylsilyloxy)bicyclo[3.3.0]oct-1-en-3-one (Table 7, entry 11). $Cp_2Ti(PMe_3)_2$ (99 mg, 0.3 mmol, 15 mol %) was added to a dry, sealable Schlenk tube in a dry box under argon. Benzene (1.5 mL) and 5-(triisopropylsilyloxy)-1-undecen-6-yne (648 mg, 2.0 mmol) were then added with stirring. After 2-3 min, a solution of *t*-$BuMe_2SiCN$ (340 mg, 2.3 mmol) in benzene (0.5 mL) was added. The tube was then sealed, removed from the dry box, and immersed in an oil bath heated to 45 °C for 16 h. General procedure C was followed for the hydrolysis and work-up to provide the desired

product. Purification by flash chromatography (ether : hexane = 5 : 95) afforded 399 mg (57% yield) of a pale yellow oil as a 1.6 : 1 mixture of diastereomers. A pure sample of the major diastereomer was obtained from the chromatography for analysis: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.8-4.9 (m, 1 H), 3.0-3.1 (m, 1 H), 2.61 (dd, J = 6.4 Hz, J = 18 Hz, 1 H), 2.1-2.2 (m, 4 H), 1.94 (dd, J = 2.8 Hz, J = 18 Hz, 1 H), 1.8-2.0 (m, 1 H), 1.2-1.4 (m, 4 H), 0.9-1.1 (m, 22 H), 0.82 (t, J = 7.1 Hz, 3 H); 13C NMR (75 MHz, $CDCl_3$): δ 211.4, 179.8, 135.9, 68.0, 42.4, 39.7, 37.4, 30.3, 28.3, 23.8, 22.8, 17.9 (two overlapping signals), 13.7, 12.3; IR (neat): 2943, 2866, 1709, 1668, 1464, 1138, 1082, 1065, 917, 883, 734, 681, 648 cm^{-1}; Exact mass calculated for $C_{21}H_{38}O_2Si$: 350.2641. Found: 350.2643. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the C-8 hydrogen at δ 4.87 gave a 5% enhancement of the adjacent hydrogens at δ 2.15 and no enhancement of the C-5 hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:



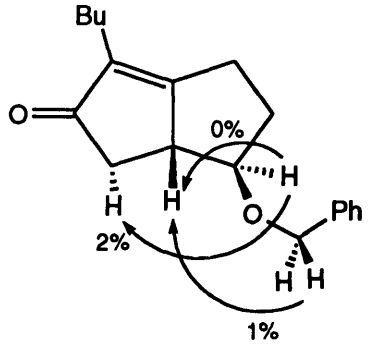
2-Butyl-9-(triisopropylsilyloxy)bicyclo[3.4.0]non-1-en-3-one (Table 7, entry 12). To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (99 mg, 0.3 mmol, 15 mol %) under argon was added benzene (1.5 mL) and 6-(triisopropylsilyloxy)-1-dodecen-7-yne (672 mg, 2.0 mmol). A solution of *t*-$BuMe_2SiCN$ (340 mg, 2.3 mmol) in toluene (0.5 mL) was then added, and the tube was sealed and immersed in an oil bath heated to 45 °C for 22 h. General procedure C was followed for the hydrolysis and work-up to provide the desired product as a single diastereomer. Purification by flash chromatography (ether : hexane = 7 : 93) afforded 390 mg (54% yield) of a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.94 (t, J = 2.3 Hz, 1 H), 3.0-3.1 (m, 1 H), 2.52 (dd, J = 6.5 Hz, J = 19 Hz, 1

H), 1.9-2.3 (m, 5 H), 1.91 (d, J = 19 Hz, 1 H), 1.2-1.6 (m, 6 H), 0.9-1.1 (m, 22 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 175.1, 135.9, 65.0, 41.4, 36.3, 35.8, 35.7, 30.9, 22.8, 22.7, 19.4, 18.0, 17.9, 13.8, 12.3; IR (nujol): 2939, 2865, 1706, 1653, 1464, 1179, 1118, 1083, 1027, 882, 681 cm^{-1}; Exact mass calculated for $C_{22}H_{40}SiO_2$: 364.2797. Found: 364.2801. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the C-9 hydrogen at δ 4.94 gave a 5.5% enhancement of the adjacent hydrogens at δ 1.43 and no enhancement of the C-5 hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:



2-Butyl-6-(benzyloxy)bicyclo[3.3.0]oct-1-en-3-one (Table 7, entry 13). Procedure C was followed to convert 3-(benzyloxy)-1-undecen-6-yne (512 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether : hexane = 1 : 4) afforded 239 mg (42 % yield) of a pale yellow oil as a 12 : 1 mixture of diastereomers. A pure sample of the major diastereomer was obtained from the chromatography for analysis: ^1H NMR (300 MHz, $CDCl_3$): δ 7.2-7.4 (m, 5 H), 4.56 (s, 2 H), 3.54 (q, J = 7.4 Hz, 1 H), 2.92 (m, 1 H), 2.0-2.8 (m, 8 H), 1.2-1.5 (m, 4 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 178.0, 138.1, 137.9, 128.3, 127.6, 127.4, 83.2, 71.7, 49.5, 41.1, 32.0, 30.0, 23.9, 23.2, 22.5, 13.7; IR (neat): 2956, 2931, 2870, 1705, 1662, 1454, 1358, 1117, 912, 734, 696 cm^{-1}; Exact mass calculated for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1772. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the C-6 hydrogen at δ 3.54 gave

a 2% enhancement of the C-4 hydrogen at δ 2.15 and no enhancement of the C-5 hydrogen. Also, irradiation of the benzyl protons at δ 4.56 gave a 1% enhancement of the C-5 hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:



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