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UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

# TITANOCENE-CATALYZED STEREOSELECTIVE COUPLINGS OF ALDEHYDES

A Dissertation
SUBMITTED TO THE GRADUATE FACULTY
in partial fulfillment of the requirements for the
degree of
DOCTOR OF PHILOSOPHY

By
MELINDA S. DUNLAP
Norman, Oklahoma
1999

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# TITANOCENE-CATALYZED STEREOSELECTIVE COUPLINGS OF ALDEHYDES

A Dissertation APPROVED FOR THE
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

BY

K.M. Nicholas

G Richter Addo

Ronald L Halterman

Daniel T. Glatzhofer

# ACKNOWLEDGMENTS

I am dedicating this thesis to my parents, Dr. Everett and Nancy Dunlap. I thank them for their support, understanding, and prayers through these past five years. They have always believed in me and encouraged me to reach for my dreams...no matter how outrageous or impossible they may have seemed. I could not have accomplished this goal without them.

I also wish to thank the Fossetts--Ray, my sister Tracy, and their three beautiful children, Jourdan, William, and Matthew. They have been an unpredictable, spontaneous, and exhilarating part of my life. Some of my happiest times in Norman include their weekend visits in which they made themselves "at home" in my apartment.

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# ABSTRACT

An efficient, catalytic, pinacol coupling of carbonyl species was developed. Optimization experiments with benzaldehyde as the substrate were performed. Numerous variables (metal reducing agent, catalyst, recycling agent, solvent, temperature, and mode of addition) were investigated to produce both optimal yields and diastereoselectivities. The optimal pinacol coupling reaction with benzaldehyde utilized manganese as the metal reducing agent, titanocene dichloride as the catalyst, chlorotrimethylsilane as the recycling agent, and THF as the solvent. Also, the optimal procedure was run at ambient temperature and rapid additions of benzaldehyde and chlorotrimethylsilane to the $Cp_2TiCl_2$/Mn/THF solution were made. 1,2-*Bis*(trimethylsiloxy)-1,2-diphenylethane was produced in yields of 90% and higher and diastereoselectivities ranged from 90 to 95%.

Aliphatic aldehydes were initially investigated using the optimal procedure. The yields ranged from 45 to 90% and diastereoselectivities ranged from 20 to 50%. Since the results were less satisfactory than those with benzaldehyde, modifications were made (metal reducing agent, catalyst, and recycling agent) to the optimal procedure to increase both reaction rates and selectivities. Also, additives (Lewis acids or bases) were sometimes incorporated into the pinacol reactions to improve yields and selectivities. In all of the modified couplings with aliphatic aldehydes, reaction rates were slower than the ones using the standard (optimal) procedure. Although reactions were slower, a diastereoselective acetal product (*de* as high as 70%) was oftentimes observed instead of the disilyl ether product.

A catalytic pinacol reaction that was enantioselective was also of interest. Chirality was introduced into the system by the titanium metallocene complexes employed. Three of the titanium complexes possessed tethers: Brintzinger's catalyst or ethylene*bis*-(4,5,6,7-tetrahydroindenyl) titanium dichloride **1**, (1S,7R,8R,10R)-2,5-diisopropylcyclohexane-

1,4-*bis*(1'-indenyl) titanium dichloride 3, and (1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-*bis*(4',5',7',8'-tetrahydroindenyl) titanium dichloride 4. Two sterically hindered titanium complexes were also employed: *bis*(2-menthylindenyl) titanium dichloride 2 , and 2,2-paracyclophane substituted salicylidene titanium dichloride 5. Significant enantioselectivity was observed with titanium complexes 1 and 4 which produced *ee*'s of 60 and 37% respectively. The remaining complexes showed negligible enantioselectivity. Based on the results with the five complexes tested, the ones possessing tethers and tetrahydroindenyl ligands afforded the best enantioselectivity.

Mechanistic studies were also conducted. Reactions known to generate acetal were run with an internal standard, naphthalene; and G.C. chromatograms were used to determine the amount of product (disilyl ether and/or acetal) present. Based on the product:naphthalene ratios, the concentration of disilyl ether relative to acetal was changing with time; thus, it was concluded that disilyl ether was being converted to acetal.

Also of interest was the intermediate responsible for generating a diastereoselective pinacol product. Benzaldehyde coupling reactions using chlorotrimethylsilane, and stoichiometric amounts of bi- $[Cp_2TiCl]_2$ or trimetallic $[Cp_2TiCl]_2MnCl_2$ complexes in THF were performed. The bimetallic reaction generated the disilyl ether with a *dl:meso* ratio of 29:1 (24 h). The trimetallic mediated reaction initially (2 h) produced disilyl ether with a *dl:meso* ratio of 1:1 and eventually (24 h) yielded acetal with *a dl:meso* ratio of 31:1. These results indicated that the bimetallic intermediate was responsible for the highly diastereoselective pinacol product.

Finally, kinetic experiments were designed to probe the rate determining step and the order of the reaction. The concentrations of benzaldehyde, chlorotrimethylsilane, and titanocene dichloride were all varied separately in pinacolization experiments. Naphthalene was used as an internal standard and the reactions were monitored by G.C. Results were not reproducible from one experiment to the next; therefore, no conclusions could be made from the kinetic experiments.

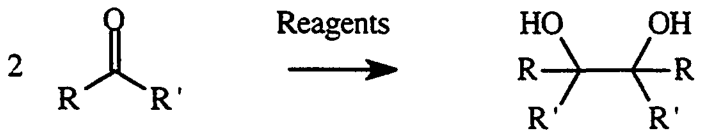
# CHAPTER 1

# PINACOL COUPLING SYSTEMS

## Background

The pinacol coupling reaction is an efficient method for generating carbon-carbon bonds with 1,2-difunctionality. Coupling can be promoted through photochemical,[1] electrochemical[2-4] or chemical means. The chemical methods used for the pinacol coupling employ a wide range of metal reductants and will be elaborated on in the course of this chapter.

**Scheme 1-1: Pinacol coupling**

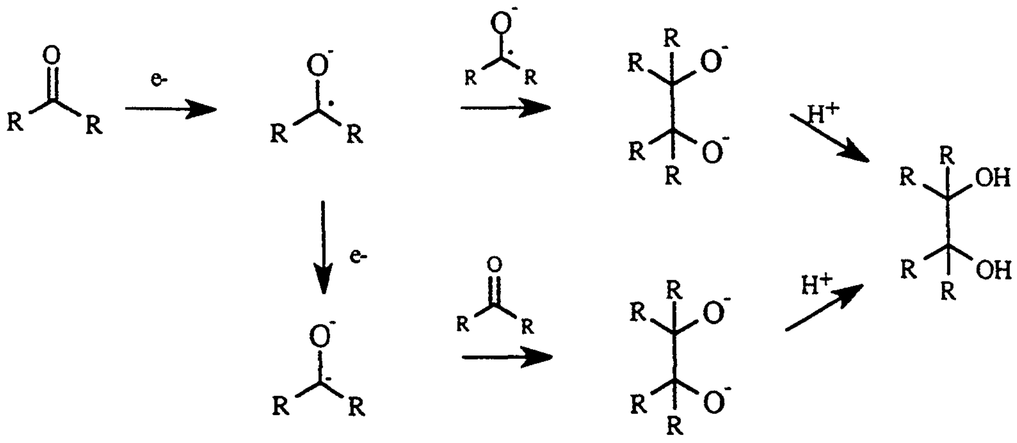


R = H, aryl, or alkyl
R' = aryl or alkyl

### *Proposed Mechanisms*

Two mechanisms have been proposed to explain the pinacol reaction. Both a radical-radical and a nucleophilic pathway have been suggested; the radical mechanism is believed to be the predominate pathway for the majority of pinacol couplings.[5] First, the ketyl radical anion is formed from the carbonyl compound with the use of a reducing agent. Once formed, the radical anion can undergo a radical-radical coupling with another radical anion to form the pinacol product, or it can be further reduced to produce the dianion. In the case of a second reduction, the dianion acts as a nucleophile and reacts with a second carbonyl group to produce the pinacol product.

**Scheme 1-2: Proposed pinacol mechanisms**



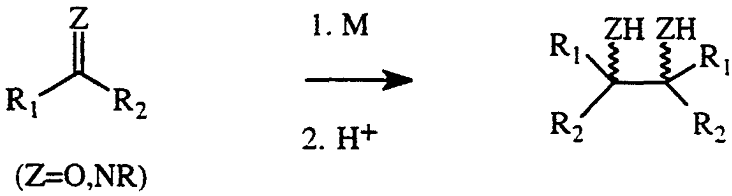
The radical-radical and nucleophilic attack mechanisms are the primary ones discussed in the literature; however, other mechanisms could be envisioned. For instance, a radical anion could react with a neutral carbonyl species to form a new carbon-carbon bond. Further reduction would lead to the pinacolate anion.

Most pinacol coupling reactions form a mixture of the *dl* and *meso* isomers when the R groups on the carbonyl moiety are different ($R_1COR_2$, $R_1 \neq R_2$). Furthermore, a common side product formed during pinacolization is the corresponding alcohol from direct reduction. Recent advances have shown that the *dl* isomer from the pinacol coupling can be selectively produced under some conditions (*vide infra*). The alcohol side product remains a problem even in some of the most recent findings and efforts are still being focused to eliminate this reduction.

### *Homo- and heterocoupling reactions*

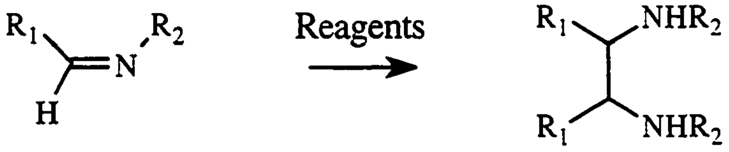
Pinacolization is capable of producing homocoupling as well as heterocoupling. In homocoupling, two identical substrates are coupled together to form a new carbon-carbon bond.

**Scheme 1-3: Homocoupling reaction**



The most common homocoupling reaction generates a 1,2-diol. The classical methods for performing this coupling employ metal reductants like Li, Na, Zn, Mg, and Al(Hg). In recent advances, early transition metal systems and lanthanides such as TiCl$_4$/M and SmI$_2$ respectively have shown to successfully generate the diol.[5] It is also possible to synthesize a 1,2-diamine by pinacol coupling of imines; however, this reaction is not as developed as the synthetic methods for the formation of the diol. The imine coupling systems developed to date provide good yields and high diastereoselectivities in some cases.

**Scheme 1-4: Homocoupling of imines**

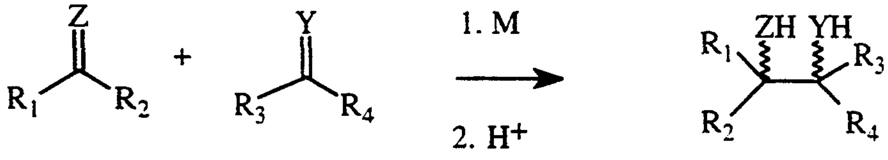


$R_1$ = phenyl
$R_2$ = aryl when reagents = Na/THF/heat
$R_2$= alkyl when reagents = TiCl$_4$/Mg(Hg)

For instance, reductive coupling using Na/THF converts N-acylimines to 1,2-diamines with yields ranging from 69 to 100%. The *dl:meso* ratios for these couplings ranged from 70:30 to 99:1.[6] N-alkylimines have also been shown to couple to the diamine. Using TiCl$_4$/Mg(Hg), the 1,2-diamine is formed in yields from 40-75% with *dl:meso* ratios as high as 9:1.[7]

In heterocoupling, two different substrates are coupled together.

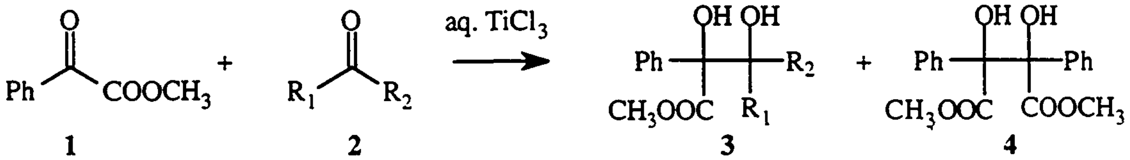
**Scheme 1-5: Pinacol heterocoupling**



The heterocoupled pinacol product has been seen in the form of unsymmetrical diols as well as amino alcohols.[5] The steric and/or electronic differences between the two substrates to be coupled are critical for the success of heterocoupling. If the differences are too great or even too small, the probability of homocoupling instead of the desired heterocoupling increases. Hence, in tailoring a cross coupling reaction, the substrates must be carefully chosen to favor the mixed pinacol product as opposed to the dimeric one.

Cross coupling of carbonyl substrates has been achieved by manipulating steric factors. Clerici and Porta achieved high degrees of cross coupling with aqueous $TiCl_3$.[8]

**Scheme 1-6: Heterocouplings mediated by aqueous TiCl3**

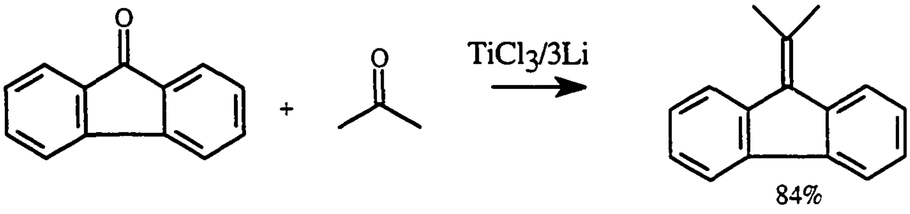


1 2 3 4

A variety of ketones 2 were evaluated with 1. A large excess of 2 ensured that minimal dimer was formed. From the results obtained, a few generalizations were made. When ketone 2 possessed bulky groups, the amount of mixed pinacol product decreased. For instance, acetophenone when coupled with 1 produced no cross coupled product 3 but only dimer 4. In contrast, less hindered ketones produced only the cross coupled product 3. Acetone was reacted with 1 and generated the cross coupled product 3 in 90% yield and showed only a trace amount of dimer **4**. In addition to examining steric features of various carbonyl substrates and their effects on cross coupling, Clerici and Porta also examined electronic features through additional functional groups attached to the carbonyl substrates. They found that additional functional groups did not direct the carbonyl substrates towards cross coupling. Heteropinacol reactions are possible based on the work presented by Clerici and Porta. However, limitations do exist. In improving the cross coupling, factors such as sterics and even electronics should be considered for both carbonyl substrates.

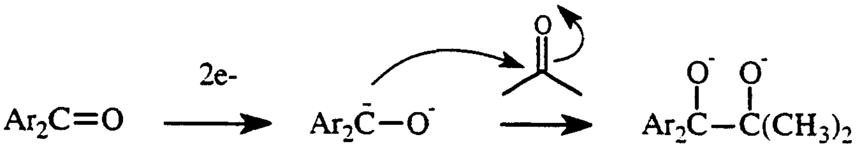
John McMurry also has investigated cross couplings of carbonyl substrates and found them to be successful when one substrate within the reaction reduces to the dianion before the other substrate reduces to the radical anion.[9] His work cross couples different ketones to yield mixed olefins. While the olefin product is not the pinacol product of interest in this dissertation, McMurry does indicate that coupling of ketones to olefins proceeds through an intermediate pinacol dianion. Since a cross coupled pinacol intermediate is occurring, the mixed olefin results will be used to provide some insight on the successes and limitations of mixed pinacol couplings. When fluorenone (Scheme: 1-7) was combined with acetone using $TiCl_3/3Li$, only the mixed coupled product was observed.

**Scheme: 1-7: Cross coupling reaction**



McMurry noted that the reduction potential of fluorenone was 1.5 V less negative than that of acetone. He suggested that aromatic ketones are chemoselectively reduced to the dianion in the presence of the aliphatic ketone. Once the aromatic substrate is reduced, it can effectively act as a nucleophile and react with the aliphatic ketone to form the mixed pinacol product.

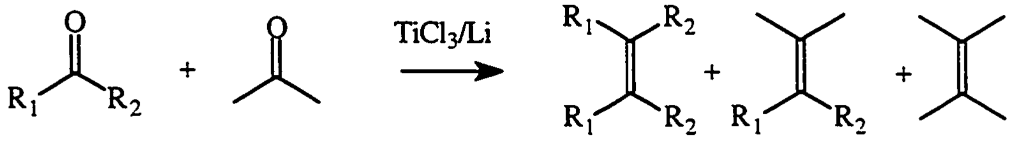
**Scheme 1-8: Mechanism for cross coupling**



Furthermore, it has been found that using an excess of the aliphatic ketone increases the probability of selectively generating the mixed pinacol product. McMurry used an acetone/ketone ratio of 4:1 to improve selectivity for the mixed coupled product over the homocoupled product.[9]

In his work with dialkyl ketones and monoaryl ketones, McMurry found that a statistical ratio of products was formed.

**Scheme 1-9: Cross coupling reaction with both mixed product and dimer formed**



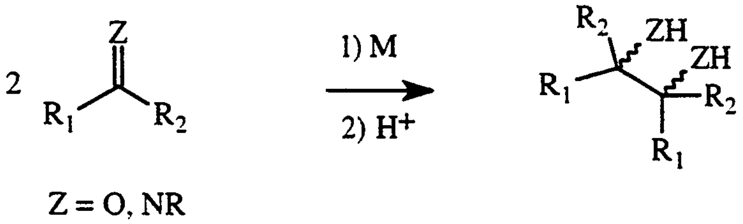
$R_1$ & $R_2$ = alkyl
$R_1$ = alkyl, $R_2$ = aryl

Since the reduction potentials of acetone and the other ketones were similar, chemoselective reduction of the ketones to the anion without affecting the acetone was not possible. Therefore, a combination of dimers and mixed products are observed.

*Inter- and intramolecular couplings*

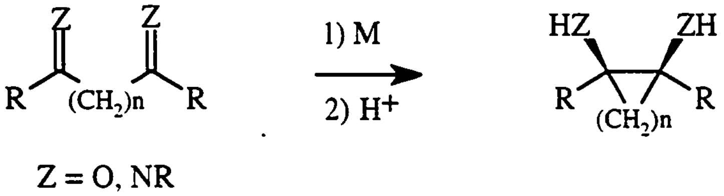
Pinacol couplings can occur intra- and intermolecularly. Extensive work has been published on the intermolecular pinacol coupling; moreover, it will be the focus of this dissertation. In intermolecular coupling, two separate carbonyl substrates react to form a new carbon-carbon bond.

**Scheme 1-10: Intermolecular coupling**



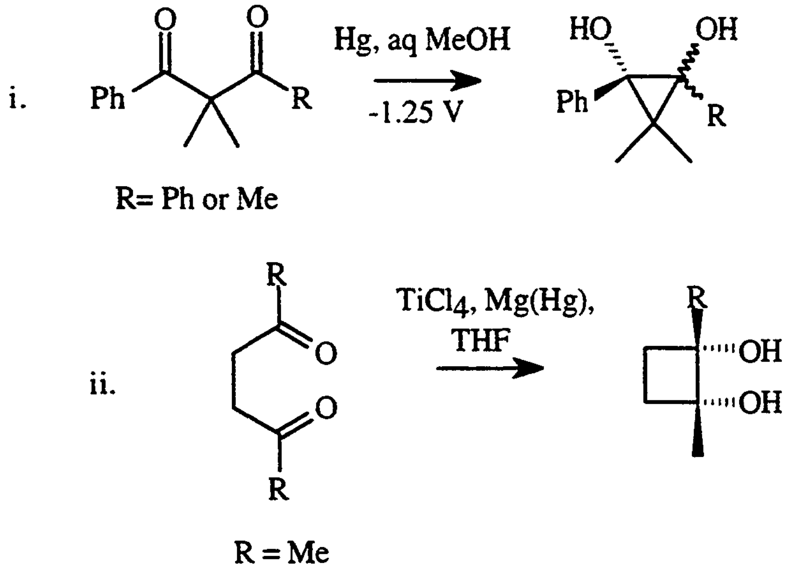
The intramolecular pinacol coupling has also been thoroughly investigated. An intramolecular coupling involves formation of the new carbon-carbon bond between two carbonyl groups in the same molecule.

**Scheme 1-11: Intramolecular Coupling**



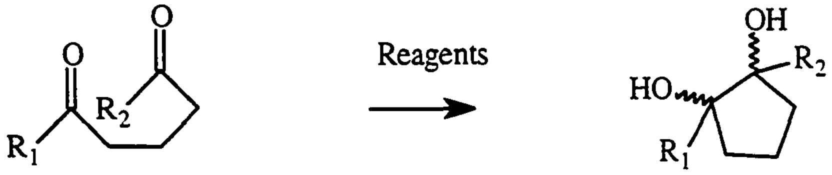
This coupling is a successful method for the construction of small rings as well as macrocyclic systems. It is argued that low valent metal reducing agents, specifically titanium, are critical to the success of the intramolecular pinacolization over such a wide range of ring sizes. The metal reducing agent acts as a template and reduces the angle strain formed during small ring closures and decreases the entropic effect during large ring closures.[5] Three membered rings have been formed (80% yield) electrochemically (-1.25 V vs. SCE) with Hg and aqueous methanol.[10] and four membered rings have been generated in 90% yield with the aid of $TiCl_4$, Mg(Hg).[11]

**Scheme 1-12: Intramolecular coupling to 3- and 4-membered rings**



Titanium trichloride in combination with metals such as zinc, zinc-copper, or potassium has been shown to intramolecularly couple carbonyl moieties to form five

**Scheme 1-13: Intramolecular couplings to form 5-membered rings**



| Reagents | $R_1$ | $R_2$ |
|---|---|---|
| $TiCl_3$, K, THF | alkyl | H |
| $TiCl_3$, Zn, pyridine,THF | alkyl | acyl |
| $TiCl_3$,Zn-Cu, DME | alkyl | alkyl |

membered rings in yields ranging from 40-70%.[12-14] Although the intramolecular couplings using $TiCl_3$-based systems are successful, they do not show any stereoselectivity.

In addition to small and medium-sized rings, macrocyclic systems can be generated when high dilution techniques are utilized. For instance, a 14-membered, macrocyclic antibiotic, grahamimycin A, was synthesized in 35% yield. The intramolecular coupling occurs between aldehydes (14 carbons apart) within grahamimycin A using $TiCl_4$ and Zn/Cu.[15] Intramolecular pinacolizations are clearly synthetically useful in the synthesis of macrocyclic systems.

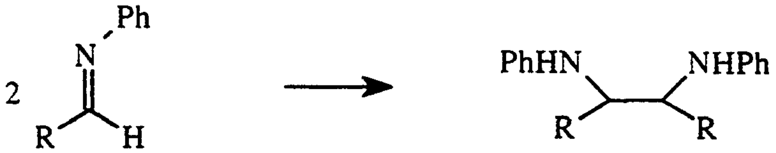
Stereoselectivity for intramolecular coupling has been achieved on a limited basis. The titanium-based systems discussed thus far for intramolecular coupling have not shown any stereoselectivity. One samarium-based system has shown high diastereoselectivity with intramolecular coupling reactions. $SmI_2$ produced cyclopentane diols with a *dl:meso* ratios ranging from 35:1 to 200:1.[16] The $Sm^{+3}$ chelated to the developing diolate thus ensuring high stereoselectivty. While it is clear that stereoselectivity can be achieved in intramolecular couplings, it should be noted that the high selectivity using $SmI_2$ is not observed with other reagents used in intramolecular couplings.

*Pinacol coupling of non-carbonyl substrates*

Pinacol couplings are applicable to a variety of substrates. In addition to the coupling of carbonyl substrates such as aldehydes and ketones, the pinacol is capable of coupling imines as well as thiocarbonyls. The coupling of imines generates vicinal diamines while the coupling of thiocarbonyls produces alkenes, not the 1,2-thiol compound. Formation of the alkene product in the thiocarbonyl coupling is thus analogous to the McMurry coupling.

The pinacol coupling of two imines generates a 1,2-diamine. Metal reducing agents such as Na[17] and $NbCl_4(THF)$[18] have proven fruitful for imine pinacol coupling.

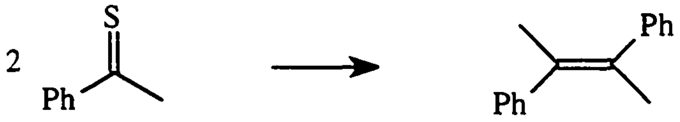
**Scheme 1-14: Coupling of imines**



Moreover, the *dl:meso* ratio achieved in these instances was higher for the vicinal amines than for the diol counterparts.[17] Low valent titanium reagents have also been used to couple imines; $TiCl_4$/Mg(Hg) yields the 1,2-diamine but with limited diastereoselectivity.[7]

Thiocarbonyl couplings, also known as the Gatterman reaction, can be affected under a range of conditions. The most recent systems utilized for this reductive coupling include: copper powder in DMSO,[19] $FeCl_3/NaBHEt_3$,[20] $TiCl_3/K$[21] and $MgC_8$.[22]

**Scheme 1-15: Coupling of Thiocarbonyls**



Also, conjugated electron withdrawing groups are necessary on the thiocarbonyl substrate to induce effective coupling.

*McMurry-Type Couplings*

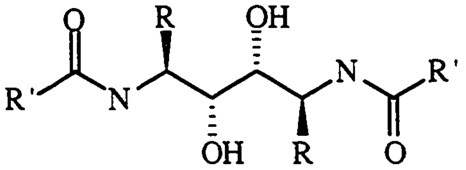
Low valent titanium species have been employed in the reductive coupling of aldehydes and ketones to alkenes. In fact, the mostly widely used systems for these

McMurry couplings utilize titanium reagents.[5] The McMurry reaction proceeds through a pinacol-like intermediate to reach the alkene product. The pinacol product can be isolated from a McMurry reaction provided that the reaction is halted early enough. In general, the McMurry coupling reaction uses conditions that are thought to produce titanium in the 0 or +1 state. These oxidation states differ from the reduced titanium species in the pinacol reactions (+3 and +2). The lower oxidation state of the titanium clearly forces the reaction to proceed past the initial pinacol coupling and eliminate to produce the alkene.

*Significance of the pinacol reaction*

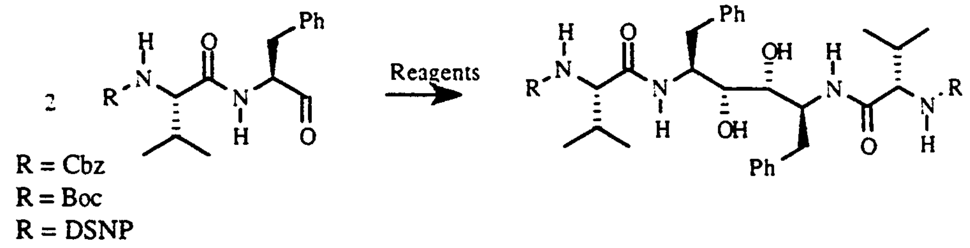
The importance of the pinacol reaction lies in its ability to generate homo as well as hetero 1,2-difunctionality. This 1,2-functionality in the form of diols, diamines, and amino alcohols is observed in variety of biologically active compounds. For instance, $C_2$-symmetrical HIV-protease inhibitors possess 1,2-difunctionality that can be generated *via* the pinacol coupling. Studies have indicated that vanadium (II) and niobium (III) systems induce the pinacol coupling of peptide aldehydes to yield $C_2$-symmetrical polyfunctional diols.[23]

**Figure 1-1: $C_2$ HIV and renin protease inhibitors**



Through the symmetrical coupling of the aldehyde unit, the 1,2-diol is formed. Moreover, introduction of all four stereocenters in the protease inhibitor can be controlled.

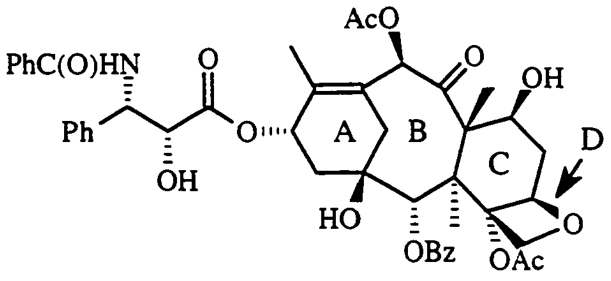
**Scheme 1-16: Formation of 1,2-diol in renin protease inhibitor**



Reagents: $VCl_3$, Zn, 1,3, dimethyl-2-imidazolidinone, THF, reflux, 70%
or $[NbCl_3(DME)]$, THF, reflux 40%

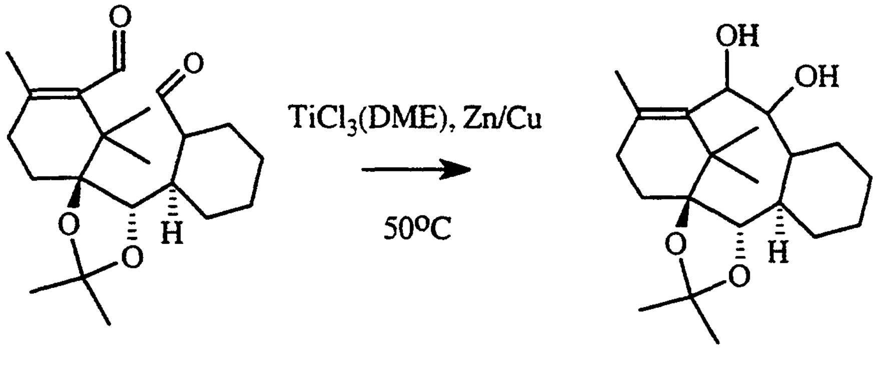
Other medicinally important molecules have been generated from the pinacol coupling. For instance, the pinacol reaction has been employed for the intramolecular coupling that forms ring B in taxol.[24]

**Figure 1-2: Taxol**



Under high dilution conditions, a dialdehyde intermediate of taxol couples in the presence of $TiCl_3$/Zn-Cu at 50°C to form the tricyclic taxoid skeleton in 40% yield (Scheme 1-17). No stereoselectivity was achieved; a mixture of the two diastereomers was isolated.

**Scheme 1-17: Formation of 1,2-diol in taxol**



The pinacol coupling reaction clearly is applicable to the synthesis of a few biologically active molecules. This reaction was used in the synthesis of both a renin protease inhibitor and taxol. In the case of the protease inhibitor, stereoselectivity was achieved. The pinacol reaction used in the synthesis of taxol did not produce any stereocontrol. While these initial cases have indicated the usefulness of the pinacol reaction, it should be noted that several limitations still exist.

*Limitations*

The lack of stereocontrol in the pinacol coupling of taxol was a primary example of a limitation. Achieving a diastereoselective as well as enantioselective product is often critical in the synthesis of biologically active molecules. The initial work with the protease inhibitor indicated that a diastereoselective pinacol product is possible; however, the absence of selectivity in the taxol molecule revealed that the problem of stereocontrol in the pinacol reaction has yet to be solved. Since the focus of stereocontrol has been directed towards achieving diastereoselectivity, the issue of enantioselectivity has not been thoroughly addressed. Thus, enantioselectivity in the pinacol coupling is also a limitation.

Another limitation of the pinacol reaction is functional group tolerance. Biologically active molecules of interest often possess multiple functional groups, all of which must withstand the reaction conditions necessary to perform a synthetic step. With a complex molecule, the pinacol reagents employed could potentially react with other functional groups on the molecule thus forming a product other than the pinacol.

The pinacol reaction has been useful in the synthesis of some biologically active molecules; however, several limitations still exist. Additional synthetic methodology would be beneficial in fine tuning the pinacol reaction. Through optimization studies, improved stereocontrol as well as functional group tolerance could be achieved. Once optimal conditions are developed, additional biologically active molecules might benefit from the pinacol reaction.

### *Pinacolizations by transition and lanthanide metal reducing agents*

A number of one electron metal reductants have been employed in the pinacol reaction. Both vanadium (II) and chromium (II) salts convert aromatic aldehydes to the expected diols.[25,26] Iron systems including $Fe(CO)_5$ and $Fe_3(CO)_{12}$ in pyridine are capable of coupling aromatic aldehydes in good yield.[27,28] As for low-valent cerium and samarium diiodide, they are capable of performing the pinacol coupling on both aromatic and aliphatic aldehydes.[12,29] And finally, titanium-based reagents have been employed extensively in the pinacol reaction.[5] The types of titanium-based compounds investigated thus far will be elaborated upon since this research project has primarily utilized titanium-based systems.

### *Pinacolizations by Lanthanides*

Several lanthanide-based systems have proven to successfully generate pinacol products. Samarium diiodide is capable of both inter- and intramolecular pinacol couplings. Intermolecular couplings of aromatic and aliphatic aldehydes with $SmI_2$ are achieved in yields ranging from 66 to 95%.[29] No diastereoselectivity is produced with the $SmI_2$ intermolecular couplings; however, high diastereoselectivity is achieved with intramolecular couplings, particularly 5-membered rings. Samarium diiodide also has an added feature of being chemoselective. It will selectively react with carbonyl species in the presence of carboxyl, cyano, or nitro groups.

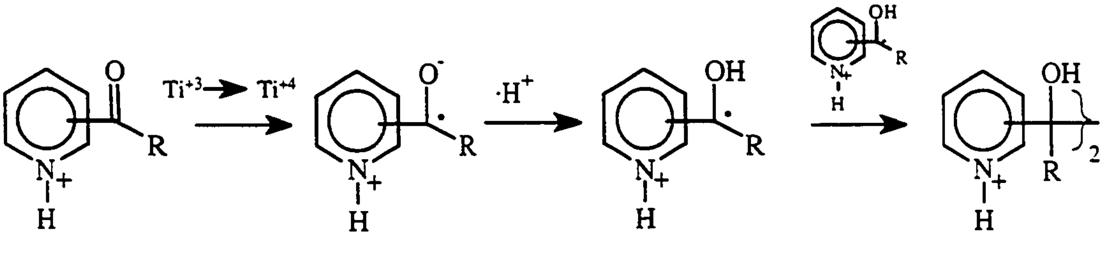
Low valent cerium has been employed in the intermolecular couplings of both aromatic and aliphatic substrates and has produced yields as high as 91%.[12] The $CeI_2$-based system, like the samarium one, is chemoselective. Carboxyl, cyano and vinyl halide groups are unaffected by this lanthanide reagent. Hence, multifunctionality may be present on the aromatic or aliphatic substrate that is to be coupled.

*Pinacolizations via Titanium Reagents*

*Titanium trichloride systems:* Titanium trichloride has been employed in several instances to induce pinacol couplings. Stoichiometric amounts of $TiCl_3$ in aqueous media,[30,31] and in $CH_2Cl_2$[32] induce pinacol couplings of aromatic aldehydes, ketones, and pyridinyl ketones.

$TiCl_3$ in aqueous medium has been shown to effect the pinacol coupling of aromatic aldehydes and ketones as well as pyridinyl ketones.

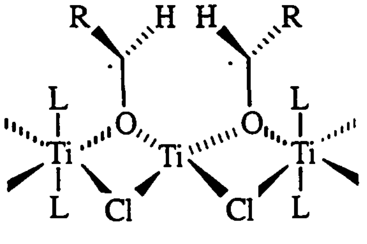
**Scheme 1-18: Coupling of pyridinyl ketones**



For instance, Clerici and Porta reported enhanced reactivity of $TiCl_3$ in basic media.[30] With a pH between 10-12, reductive coupling occurs to produce the pinacol product. Reactions times were approximately five minutes and yields were listed as 95% for aromatic ketones. Diastereoselectivities were minimal; however, for aromatic aldehydes, the *dl/meso* ratio was 1.3:1 and for ketones, it was 2.7:1. Clerici and Porta also investigated $TiCl_3$ in acidic media, specifically, acetic acid.[31] With the acidic media, pyridinyl ketones were found to successfully undergo coupling. Simple aromatic aldehydes and ketones failed under these conditions. Pinacol yields range from 72 to 86% and *dl/meso* ratios were 1.7:1 at most.

$TiCl_3$ also induces pinacol coupling in organic solvents such as methylene chloride. Clerici and Porta again demonstrated that pinacol coupling could occur with a variety of aromatic aldehydes using this titanium reagent.[32] Yields ranged from 35 to 96% and stereoselectivites, in most cases, were >100:1. While Clerici and Porta have proven that pinacol couplings can occur in both aqueous and organic media; it is clear that the organic media possess the additional advantage of producing diols stereoselectively. It was hypothesized that a trimetallic intermediate is responsible for the high diastereoselectivity observed.

**Figure 1-3: Titanium trimetallic intermediate**



The oxygens from the carbonyl moieties coordinate to the titanium atoms. Because of steric hindrance, the R groups on the carbonyl species will be *anti* to one another; hence, high diastereoselectivity can be achieved.

*Titanium reagents in combination with reducing agents:* A variety of titanium reagents ($TiCl_x$) have been employed along with reducing agents to generate an active titanium intermediate capable of inducing the pinacol coupling. For instance, the combination of $TiCl_4/Zn$ is capable of reductively coupling both aromatic and aliphatic aldehydes and ketones to form the diol.[33] A combination of $TiCl_3/Mg$ developed by Trylik yields alkenes with aromatic substrates. However, when aliphatic substrates were employed, pinacols were produced in moderate yield.[34] $TiCl_3$ with $LiAlH_4$ has also been employed but generates the alkene product instead of the pinacol.[21]

Some titanium/reducing agent systems have shown high diastereoselectivity in addition to good pinacol yields. $TiCl_4$ in combination with $Bu_2Te$ in DME promotes the pinacol coupling of aromatic aldehydes with good *dl* selectivity.[35] Furthermore, $TiCl_4$ in the presence of nBuLi also promotes the pinacol coupling of aldehydes with some *dl* selectivity.[36] Clearly, various forms of titanium and reducing agent are capable of promoting pinacol reactions. From the latter results discussed, it is also apparent that titanium species have the potential to generate a stereoselective pinacol product.

*Titanocene($Cp_nTiX_n$)-Based Pinacol Couplings:* Titanocene-based reagents are capable of producing pinacol products stereoselectively. The various derivatives of titanocene that have displayed coupling activity include $[Cp_2TiCl]_2$,[37] and $RMgBr/Cp_2TiCl_2$.[38] These titanocene reagents were used in stoichiometric amounts to reductively couple aldehydes. A varying but high degree of stereoselectivity was achieved with each.

**Scheme 1-19: Stoichiometric amounts of Ti reagent in pinacol couplings**

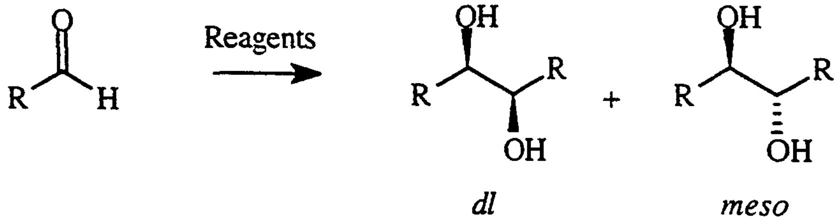


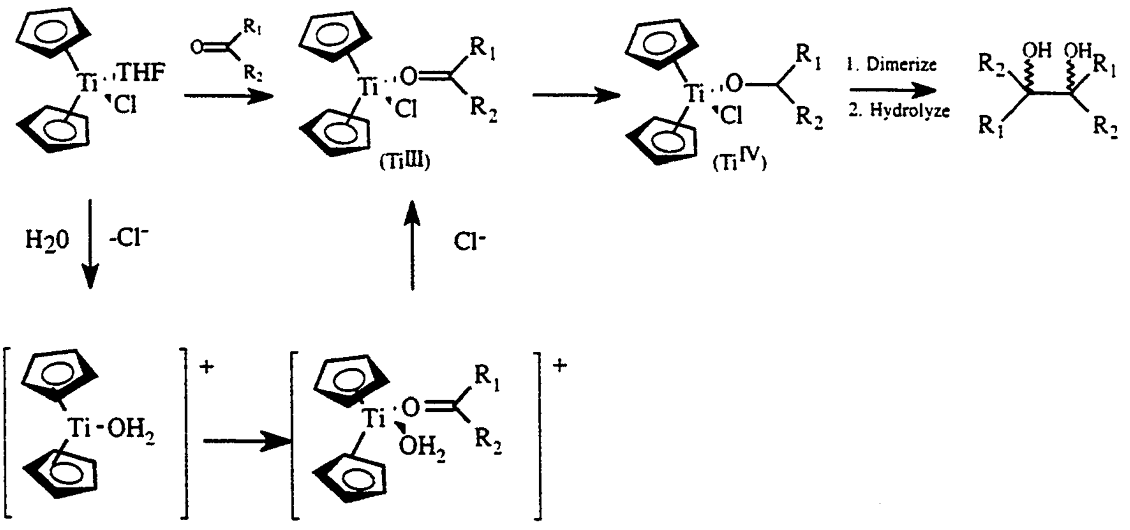
**Table 1-1: Couplings with titanocene reagents**

| Reagent: | yield | dl:meso |
|---|---|---|
| **$[Cp_2TiCl]_2$** | | |
| R= aryl | 95% | 98:2 |
| R=α,β-unsat. | 88% | 98:2 |
| **$Cp_2TiCl_2/RMgBr$** | | |
| R= aryl | 80-96% | 92:8 to 99:1 |
| R = α,β-unsat | 85-98% | 98:2 to 99:1 |

Barden and Schwartz have investigated aqueous pinacol couplings using $[Cp_2TiCl]_2$ in stoichiometric amounts.[37] Both aromatic aldehydes as well as α,β-unsaturated aldehydes were evaluated and found to undergo pinacol coupling. Yields ranged from 91-95% for aromatic aldehydes and 88% for α,β-unsaturated aldehydes. Stereoselectivity for both types of aldehydes consisted of a 98:2 *dl/meso* ratio.

Barden and Schwartz's aqueous system consisted of a THF:$H_20$ ratio that was varied from 100:0 to 50:50. Their initial experiment used a 4:1 ratio of THF to water and failed to generate any pinacol product. However, upon adding NaCl (62 equivalents/Ti) to the reaction mixture, it was found that the substrate, benzaldehyde, was completely consumed. In the presence of the NaCl additive, it was discovered that the pinacol couplings were successful (for benzaldehyde, yield: 85%, *dl:meso* 95:5) even in the extreme case of a 50:50 mixture of THF and water. A mechanism was proposed to rationalize the role of the NaCl in the reaction:

**Scheme 1-20: Mechanism for pinacol coupling using $[Cp_2TiCl]_2$**



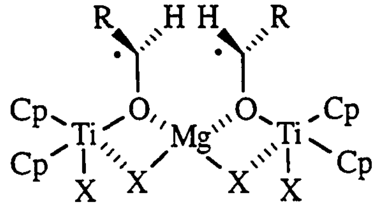
In the absence of water, the carbonyl moiety coordinates to the titanocene compound in the +3 state. Electron transfer between the titanium and oxygen yields a titanium species in the +4 state. Dimerization of two of these species through radical coupling will eventually generate the pinacol diol. It was suggested that the sterically crowded environment produced when two of the Ti(IV) species come together is responsible for the high diastereoselectivity seen.

In the presence of water, the initial titanocene species has the option of undergoing ligand exchange to produce the cationic hydrated species. It was speculated that this cation can also coordinate to the aldehyde. Moreover, the presence of additional $Cl^-$ allows a $H_2O/Cl^-$ ligand exchange to occur and generate the Ti(III) species needed to undergo the reductive coupling. As stated earlier, in the absence of NaCl, the aqueous reaction does not lead to reductive coupling. Barton and Schwartz have clearly indicated the usefulness of a stoichiometric amount of their titanocene reagent in generating pinacol products. Their system has applications to a variety of aldehydes and has shown high diastereoselectivites in all cases. Moreover, they have done initial work illustrating that these coupling reactions can occur in the presence of water.

Handa and Inanaga found that pinacolization of aromatic and α,β-unsaturated aldehydes can occur using stoichiometric amounts of titanocene dichloride in the presence of a Grignard reagent.[38] A variety of reducing agents were evaluated in combination with titanocene dichloride including $SmI_2$, zinc metal, and i-PrMgI. The samarium diiodide and zinc reducing agents produced a *dl:meso* ratio of 11:1 for hydrobenzoin. When the Grignard reagent was employed as reducing agent, the *dl:meso* ratio was 80:1. As mentioned earlier, a variety of substrates were evaluated. Aromatic aldehydes, when reacted with $Cp_2TiCl_2$/sec-BuMgCl, produced pinacol yields ranging from 50 to 96% and *dl:meso* ratios from 100:1 to 11:1. The yields with α,β-unsaturated aldehydes ranged from 87 to 96% and diastereoselectivities from 100:1 to 60:1. Aliphatic aldehydes were also evaluated but failed to react under the conditions described by Handa and Inanaga.

Handa and Inanaga rationalized the high stereoselectivity by suggesting the involvement of a trimetallic intermediate. The Ti-Mg-Ti/2RCHO intermediate suggested places the R groups from the coordinated aldehydes *anti* to one another to reduce the amount of steric hindrance. With the R groups *anti* to one another, the *dl* pinacol product is generated. Titanocene reagents have clearly proven successful at not only generating the pinacol product but also at achieving it with high diastereoselectivity.

**Figure 1-4: Titanium/magnesium trimetallic intermediate**



The trimetallic intermediate suggested by Handa and Inanaga is structurally similar to a trimetallic complex that has been synthesized using $Cp_2TiCl_2$ and magnesium (and several other metallic reductants) in a 2:1 ratio.[39]

**Scheme 1-21: Synthesis of trimetallic complex**

The synthesis and characterization of the trimetallic complex in Scheme 1-21 proves that trimetallic species are synthetically possible and thus supports Handa and Inanaga's explanation for stereoselectivity.

*Structural features of hindered titanocene complexes*

Titanium (III) metallocene complexes, in general, form dimers in the solid and solution phase.[40] However, some of the more hindered titanium complexes evaluated in this study have been reported as monomers in the solid state. With less hindered complexes, dimers are observed in the solid state, and it is assumed that they will be capable of forming dimers in solution. Both $(Me_5Cp)_2TiCl_2$ and $(t\text{-}Bu_2Cp)_2TiCl_2$, when reduced to the +3 state, do not form dimers in the solid state but are monomeric due to the bulky groups on the cyclopentadienyl rings.[40] The evidence for monomers with these two complexes was established in the solid state by X-ray and does not necessarily indicate that in solution phase a monomer instead of a dimer will exist. However, when compared to other titanium-based complexes, the monomer state for the above catalysts in the solid state (and likely solution) is unique and therefore could possibly lead to a different intermediate in the solution reaction phase.

## Conclusion

The pinacol reaction has been utilized to generate a carbon-carbon bond through a variety of different means including photochemical, electrochemical, and chemical. As mentioned previously, two mechanisms have been proposed to interpret the reaction--radical and nucleophilic attack. To date, the majority of reactions appear to occur *via* the radical pathway.

The pinacol reaction is extremely versatile. Both homo- and heterocoupling reactions have been reported. Furthermore, inter- and intramolecular couplings occur to produce unique 1,2-difunctionality. The variety of functionality that can be produced through this reaction has already proven beneficial in the synthesis of some biologically active molecules; and will potentially contribute to the synthesis of more important molecules.

Some limitations to the pinacol reaction should be briefly recapped. The classical methods for pinacol coupling (Na, Mg, and Al) use strong reductants which tolerate few functional groups. Moreover, many of the classical methods do not provide any stereoselectivity. Recent work has indicated that low valent transition metals are capable of inducing the pinacol coupling with stereoselectivty and are not as harsh as the classical methods. Some selectivity has been achieved with low valent metals like titanium and vanadium complexes. In the majority of these cases, stoichiometric amounts of these low valent transition metals (alone or in combination with a stoichiometric amount of a 2e- reducing metal) are necessary. Only in the last few years have catalytic amounts of these low valent transition metals (in combination with a stoichiometric reducing metal) been used to perform the pinacol coupling.

The versatility of the pinacol coupling is subjective to the substrate employed. Aromatic substrates are more readily coupled than aliphatic ones and hence result in higher yields. Stronger reductants and harsher conditions are necessary to couple aliphatic substrates. Another common problem in the pinacol coupling is the direct reduction of the carbonyl substrate to the corresponding alcohol. This problem has been observed with the classical methods as well as with the most recent systems using low valent transition metals. Finally, cross coupled pinacol reactions have not been fully developed yet. Chemoselective issues remain constant in cross coupling reactions. Statistical amounts of the two dimers and the mixed pinacol product persist in cross coupling reactions: and additional work is necessary to develop an approach that favors the cross coupled product.

In addition to coupling aldehydes and ketones, the pinacol reaction is applicable to a variety of other substrates including imines and thiocarbonyls. The coupling of imines leads to vicinal diamines with, often times, improved diastereoselectivity over the corresponding diols. Thiocarbonyls also undergo coupling with the use of certain reducing conditions. The thiocarbonyl coupling reactions do not stop at the disulfur compound but proceed to the alkene.

The McMurry coupling reaction also generates a carbon-carbon double bond. During the McMurry reaction, a pinacolate intermediate is formed but is eventually converted into the alkene. The lower oxidative state of the reducing metal in the McMurry coupling is responsible for the reaction continuing all the way to the alkene as opposed to stopping at the diol.

Numerous one electron metal reducing agents generate the pinacol product. Titanium is one of these metals that has shown considerable success in pinacolizations. $TiCl_3$ in various media, and other titanium reagents in the presence of reducing agents have produced the pinacols in high yield, and in some instances, have shown high diastereoselectivities as well.

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# CHAPTER 2

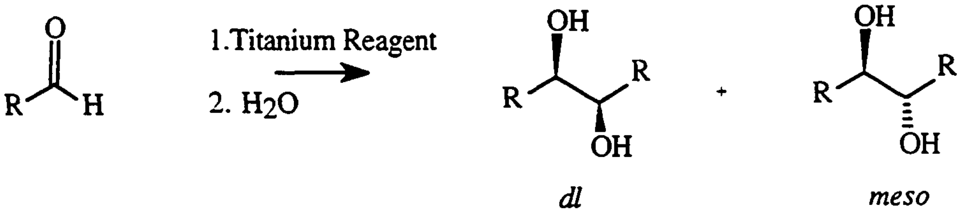
# OPTIMIZATION EXPERIMENTS FOR METALLOCENE-CATALYZED, STEREOSELECTIVE PINACOL COUPLINGS

## Introduction and Background

### *Conceptual basis for project*

Several literature precedents were utilized in developing the catalytic pinacol system. Numerous titanium-based reagents when used in stoichiometric amounts have been shown to produce pinacol products diastereoselectively. Titanium trichloride homocouples aromatic ketones and aldehydes to produce primarily the *dl* diol.[1-4] Furthermore, reduced titanocene complexes in stoichiometric amounts selectively produce the *dl* pinacol product from aromatic and α,β-unsaturated aldehydes.[5,6]

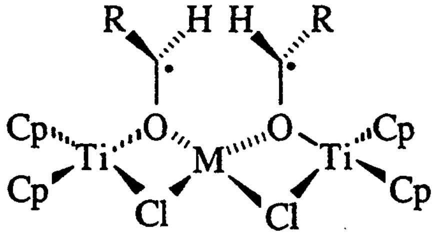
**Scheme 2-1: Pinacol reactions using stoichiometric amounts of titanium reagents**



Through a one electron process, a titanium (III) reagent is presumed to reductively couple with the carbonyl substrate; and, subsequently a radical-radical coupling of the two carbonyl species occurs to produce a titanium pinacolate intermediate. Aqueous work-up is used to hydrolyze the titanium pinocolate and yield the final diol product and a titanium oxide side product. The titanium (IV) oxide is extremely stable and incapable of performing the reductive coupling step again. Hence, a stoichiometric amount of titanium reagent is necessary as long as an aqueous work-up is employed. A more detailed description of this process can be found in chapter one.

The diastereoselectivity observed with the titanium reagents has been interpreted in terms of a bi- or trimetallic intermediate.

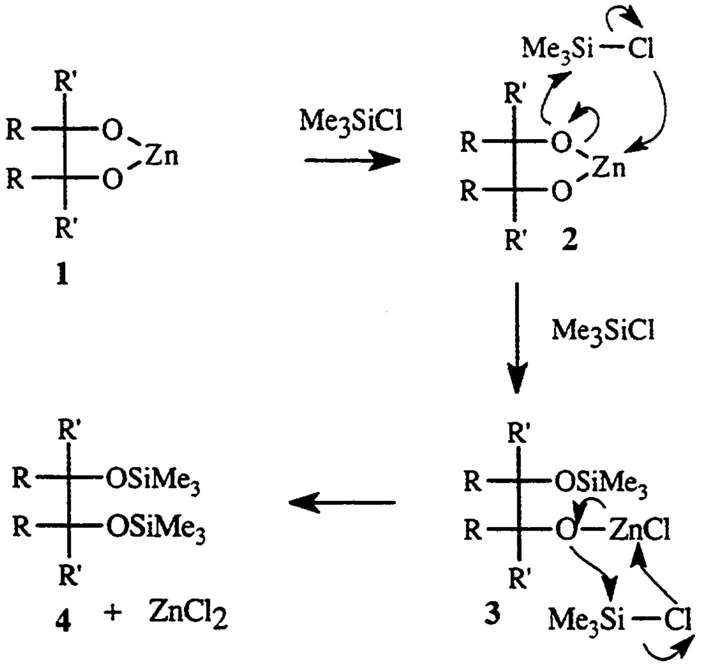
**Figure 2-1: Trimetallic intermediate coordinated to substrate**



The R groups on the carbonyl moieties position themselves *anti* to one another to reduce the amount of steric hindrance. With these groups *anti* to one another, the *dl* isomer will be generated upon cleavage of the titanium-oxygen bonds.

Another system recently reported utilized TMSCl, zinc metal, and ultrasound to induce pinacol coupling.[7] Presumably, the high energy sound waves that pass through the solution clean the surface of the zinc metal. Through this interaction, liquid-phase molecules are capable of coming into closer contact with the zinc. In contrast to the titanium-based pinacol reactions discussed earlier, this reaction generates disilyl ethers instead of diols and is applicable to both aromatic aldehydes and ketones. Unlike the titanium systems mentioned earlier, the TMSCl/Zn reaction does not exhibit appreciable stereoselectivity. The role of TMSCl may be envisioned through the following suggested mechanism:

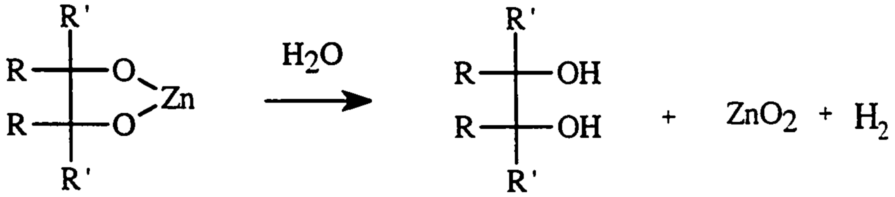
**Scheme 2-2: Suggested mechanism for TMSCl/Zn pinacol system**



The zinc metal induces pinacol coupling to yield a metal pinacolate, **1**. Then, TMSCl reacts with this intermediate *via* electrophilic substitution replacing the zinc-oxygen bond with a silicon oxygen bond. Two molecules of TMSCl react with one pinacolate molecule to produce the disilyl ether **4** and $ZnCl_2$.

When water is used to cleave the metal-pinacolate intermediate instead of TMSCl, the following acid/base reaction is envisioned:

**Scheme 2-3: Cleavage of metal-oxygen bonds in aqueous work-up**



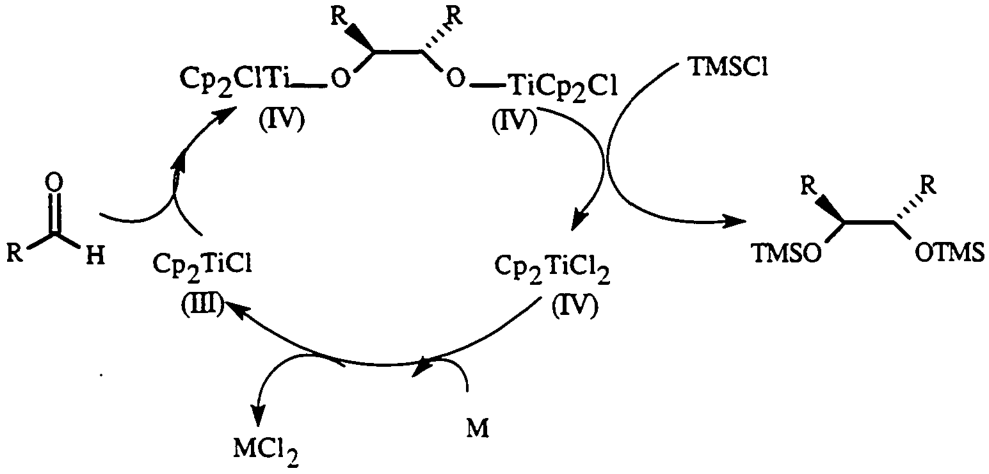
The diol is generated instead of the disilyl ether as seen in the Zn/TMSCl system. Also, zinc oxide is produced instead of zinc chloride. In the pinacol systems discussed in chapter one, stoichiometric amounts of titanium reagents ($TiCl_3$ or $Cp_2TiCl_2$) were used because the aqueous work-up generates inert titanium (IV) oxide. If TMSCl were used in combination with one of these titanium reagents, the titanium side product would be a titanium (IV) chloride species that, after reduction, could be capable of reacting with more substrate.

## Objective

The pinacol synthetic methodology project has focused on achieving three goals. The first goal was to develop a pinacol reaction that was catalytic in the metallocene. The second objective was for the pinacol reaction to generate the product stereoselectively. Initial work focused on achieving diastereoselectivity; later studies investigated enantioselectivity. And finally, the third aim was for the pinacol reactions to be applicable to a variety of substrates.

The titanocene systems that specifically generated the *dl* isomer and the Zn/TMSCl system were the conceptual basis for development of a metallocene-catalyzed, stereoselective pinacol reaction (Scheme 2-4).

**Scheme 2-4: Catalytic cycle for pinacol coupling**



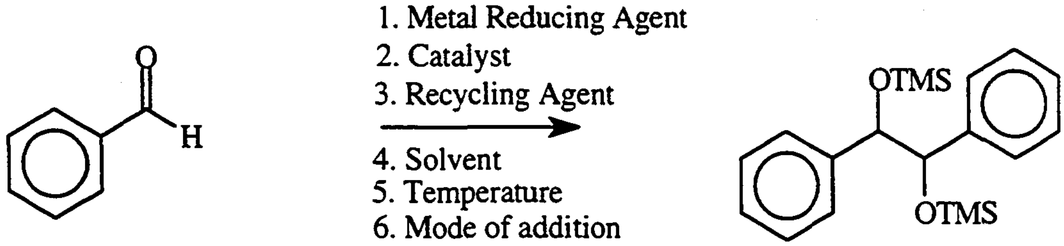
A stoichiometric amount of metal reducing agent will be employed to reduce the titanocene dichloride from its +4 state to the active +3 state. Once in the +3 state, the titanocene (III) chloride should be capable of reductively coupling with the carbonyl substrate to produce a titanium pinacolate intermediate. The TMSCl would then act as a recycling agent to regenerate the titanocene dichloride in the +4 form and to yield the disilyl ether product.

## Results and Discussion

### *Optimization Experiments*

The initial work with the pinacol synthetic methodology project focused on developing an optimal, catalytic procedure for the aromatic substrate, benzaldehyde.

**Scheme: 2-5: Six variables investigated**



Numerous variables were examined including: reducing metal, recycling agent, catalyst, temperature, solvent, and modes of addition. Activated 4 Å molecular sieves were used in all of the reactions to ensure that the reaction medium remained anhydrous.

*Metal Reducing Agents:* A stoichiometric amount of a metal reducing agent is necessary in the catalytic pinacol reaction. Several criteria were used in determining which metal reducing agents to evaluate. First, it is critical that the metal be a strong enough reductant to reduce the metallocene catalyst from its +4 state to the active +3 state, yet at the same time, not be so powerful to directly reduce the carbonyl substrate. The reduction potentials, E°, for prospective metal reducing agents have been determined in water with respect to a standard hydrogen electrode.[8]

**Table 2-1: Electrochemical Series**

| **M** | $\rightleftharpoons$ | **$M^{+n}$ + ne-** | **$E^o$/V** |
|---|---|---|---|
| Fe | $\rightleftharpoons$ | $Fe^{+3}$ + 3e- | 0.037 |
| Sn | $\rightleftharpoons$ | $Sn^{+2}$ + 2e- | 0.1375 |
| Zn | $\rightleftharpoons$ | $Zn^{+2}$ + 2e- | 0.7618 |
| Mn | $\rightleftharpoons$ | $Mn^{+2}$ + 2e- | 1.185 |
| Al | $\rightleftharpoons$ | $Al^{+3}$ + 3e- | 1.662 |
| Mg | $\rightleftharpoons$ | $Mg^{+2}$ + 2e- | 2.372 |

The metal reducing agents are listed in order of reducing capability. Iron is considered to be the weakest reducing agent while magnesium represents the strongest reducing agent within Table 2-1.

It was also of considerable interest to know the standard potentials for the substrates used in our reactions. The half wave potentials for unsubstituted aromatic aldehydes and ketones range from -1.8 to -2.0 V (one electron reduction) vs. SCE (saturated calomel electrode) in aprotic solvents like DME. Aliphatic aldehydes and ketones possess half-wave potentials from -2.2 to -2.8 V (one electron reduction) vs. SCE in aprotic solvents.[9] Although the potentials were compared to the SCE for both the aromatic and aliphatic substrates, they can be converted to values for the standard hydrogen electrode or SHE (add 0.241 V to SCE value). Through extrapolation, the aromatic substrates range from -1.6 to -1.8 V vs. SHE and the aliphatic substrates range from -1.9 to -2.6 V vs. SHE.

Both the carbonyl substrates and the metal reducing agents can be compared to one another using the potentials from the SHE electrode. Iron through manganese (0.037 V to 1.185 V vs. SHE) are not thermodynamically capable of reducing the aromatic or aliphatic substrates whose lowest reduction potential is -1.6 V vs. SHE. In a reaction with manganese (1.185 V) and an aromatic substrate possessing a smaller potential, the overall redox potential is negative and therefore not spontaneous ($E^\circ = 1.185 \text{ V} + -1.6 \text{ V} = -0.415 \text{ V}$). These metals with smaller potentials should not directly reduce the carbonyl substrates based on the electrochemical data.

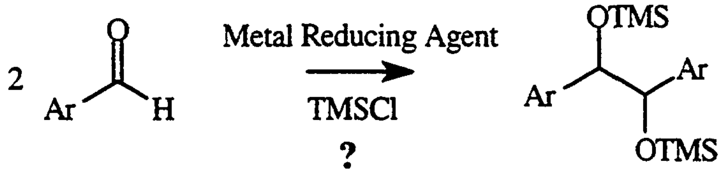
Aluminum and magnesium possess larger potentials of 1.662 V and 2.372 V vs. SHE respectively. Aluminum should be able to reduce some of the aromatic substrates with smaller potentials (-1.6 V) but will not be capable of reducing the aliphatic substrates (-1.9 V to -2.6 V). Based on its larger potential, magnesium should be capable of directly reducing all of the aromatic substrates and some of the aliphatic substrates with small potentials (less than -2.37 V). Thermodynamically, magnesium should reduce the aromatic substrate readily; and the aluminum, depending on the aromatic substrate, may or may not reduce it.

While these initial conclusions can be made based on electrochemical data, a few discrepancies should be emphasized. The potentials for the metals were determined in an aqueous environment while the potentials for the carbonyl substrates were determined in a nonpolar medium like DME. This difference raises some doubt for the thermodynamic conclusions just made. Moreover, various features about the physical condition of the metal itself might influence the reaction and yield a result contrary to what was thermodynamically predicted.

In our reactions performed with the different reducing metals (Tables 2-2, 3, and 4), results contrary to the thermodynamic data were often produced. The results from varying the reducing metals during the pinacol couplings indicated a different order of reactivity. This discrepancy was attributed to several different factors. First, the particle size of each metal varied. With the smaller particle sizes tested, a greater surface area of the metal was available to act as a reductant. Also, some of the metals were believed to be partially oxidized on the surface; and finally, the pinacol reactions were heterogeneous mixtures. The metal's insolubility in the medium influenced its effectiveness.

With all the metals tested, control reactions were performed in which the catalyst was omitted. Ideally, in the absence of catalyst, no product formation should be observed.

**Scheme 2-6: Control reaction (no catalyst present)**



If the disilyl ether was observed (*via* gas chromatography analysis) during the control reaction, then it was concluded that the metal was reducing the carbonyl substrate by itself.

Zinc was evaluated in several different particle sizes as well as at several different temperatures (Table 2-2). Benzaldehyde and TMSCl were combined with zinc in a THF medium to determine if zinc could induce coupling by itself. Both the granular (-30 to +100 mesh) and dust (-100 mesh) form of zinc reductively coupled benzaldehyde at ambient temperature in the absence of catalyst. Several temperatures were evaluated with both particle sizes of zinc to determine if the coupling could be halted during the control phase. However, in most instances, the reaction with zinc still formed a substantial amount of disilyl ether. Since disilyl ether was not formed in the control reaction using granular zinc at -78°C, titanocene dichloride was added to determine if the zinc could reduce titanium to its +3 state at such a low temperature. No product was observed one day after the catalyst was added to the reaction based on G.C. analysis.

## Table 2-2: Control reactions with Zinc metal (other components: PhCHO/ TMSCl/ THF)

| **Zinc** (particle size) | **Temperature** | **Results** (product:aldehyde)[a,b] |
|---|---|---|
| granular | -78°C | 0:1[c] |
| granular | 0°C | 1:3 |
| granular | R.T.[d] | 1:4 |
| dust | -78°C | 2:1 |
| dust | 0°C | 2:1 |
| dust | R.T.[d] | 2:1 |

[a] aldehyde:product ratios determined by gas chromatography; [b] ratios determined after reaction was in progress for one hour; [c] catalyst was added to this reaction after control reaction. [d] Room temperature (approximately 20°C).

A few hypothese could explain the failure of this reaction. First, zinc is not capable of reducing $Cp_2TiCl_2$ at -78°C. Second, the zinc does reduce the metallocene at -78°C, but one of the other steps in the catalytic pathway was sluggish or nonexistent at -78°C.

Other metals evaluated for reducing capability appeared promising during the control reactions (i.e. they did not independently induce coupling); however, they proved ineffective once the titanocene dichloride was added (Table 2-3). The results clearly do not correlate with the reduction potentials in the electrochemical series. Based on the electrochemical potential, aluminum should have been a more powerful reducing agent than the zinc evaluated earlier. In accordance with the results obtained from the zinc metal control reactions, the aluminum should have failed during the control reaction and formed pinacol product in the absence of catalyst. This contrary result is rationalized by the notion that the aluminum metal possessed a surrounding oxide layer making it ineffective in the reduction of the substrate during the control reaction as well as the titanocene in the regular reaction.

**Table 2-3: Evaluation of tin, iron, and aluminum reducing metals**[a,b,c,d]

| Metal | Product:Aldehyde |
|---|---|
| tin (control) | 0:1 |
| tin (catalyst added) | 0:1 |
| iron (control) | 0:1 |
| iron (catalyst added) | 0:1 |
| aluminum (control) | 0:1 |
| aluminum (catalyst added) | 0:1 |

[a] all metals in 0 state; [b] control reactions included PhCHO, TMSCl, THF, ambient temperature and were run for 4 h before $Cp_2TiCl_2$ was added; [c] reactions run at ambient temperature; [d] reactions monitored by G.C.

Tin and iron were originally chosen as candidates because their reduction potentials were somewhat less than that of zinc. It was thought that metals with smaller potentials would be less likely to form the pinacol product in the absence of catalyst (unlike the zinc). However, as the results indicate, tin and iron were ineffective at reducing the titanocene catalyst and therefore were not suitable candidates for our pinacol system. The different particle sizes and the state of the metals evaluated (i.e. partially oxidized therefore less reactive than listed reductive potential) may explain why the metal's reactivity did not always correlate with the reducing potential trend.

A few metals evaluated were capable of reducing the catalyst from its +4 state to the active +3 state without affecting the carbonyl substrate itself. Both manganese and magnesium were evaluated as reducing metals for our pinacol system (Table 2-4). In the control reactions, neither metal produced the pinacol product in the absence of the titanocene dichloride. Once the catalyst was added, the disilyl ether was observed in substantial amounts by G.C. analysis. These two metals differ in the pinacol yields they produced as well as the diastereoselectivities.

**Table 2-4: Manganese and Magnesium as stoichiometric reducing metals (Conditions: Metal, PhCHO, $Cp_2TiCl_2$, TMSCl, THF, ambient temperature, 20 h)**

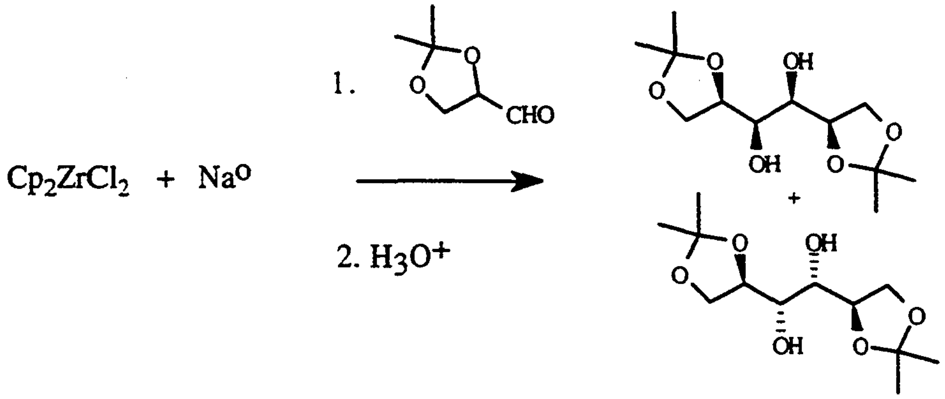
| metal | yield | dl:meso |
|---|---|---|
| magnesium[a] | 0% | na |
| manganese[a] | 0% | na |
| magnesium | 50-70% | 75:25 to 95:5[b] |
| manganese | >90% | 90:10 to 97:3 |

[a] control reactions (no catalyst present) evaluated after 20 h by GC; [b] depended on mode of addition and temperature

Six metal reducing agents were thus evaluated in stoichiometric amounts in both control and regular reactions. Some of the metals proved ineffective at reducing the titanocene to its active form (Sn, Fe, Al), and one metal (Zn) was capable of reductively coupling the benzaldehyde in the absence of catalyst. Two of the metals examined (Mn, Mg) met the desired criteria for the catalytic pinacol system; moreover, the aldehyde was completely consumed according to G.C. chromatograms. Manganese produced a significantly higher yield and *dl:meso* ratio than magnesium did. After these initial experiments with various reducing metals, manganese clearly provided the optimal results and was therefore utilized while evaluating other variables.

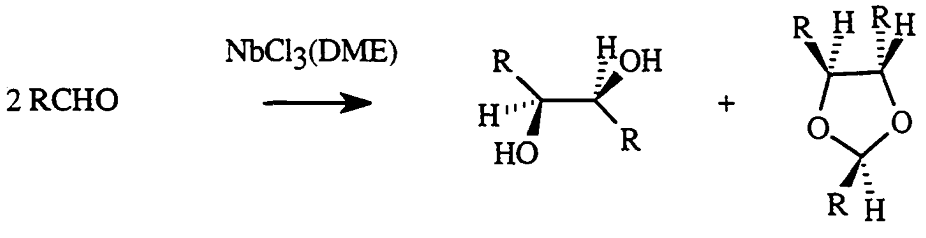
*Catalysts:* Several commercially available complexes were investigated for their ability to promote the pinacol coupling of benzaldehyde. Pinacol reactions using stoichiometric amounts of titanocene dichloride,[5,6] zirconocene dichloride,[10] or niobium trichloride [11-13] all have been reported. The work published by others during our project on reactions using catalytic amounts of titanocene dichloride will be discussed later in this chapter. As for the report on zirconocene dichloride, it was used in combination with sodium metal to perform stereoselective (*dl:meso*: 65:35) pinacol couplings on 2,3-O-isoproplidene-D-glyceraldehyde.[10]

**Scheme 2-7: Coupling of 2,3-di-O-isopropylidene-D-glyceraldehyde**



The $NbCl_3(DME)$ couples aliphatic aldehydes with high diastereoselectivity (*dl:meso* 9:1). A substantial amount of acetal was formed as well and also possessed a high *dl:meso* ratio.[11-13]

**Scheme 2-8: Pinacol coupling using niobium reagent**



Based on the literature precedents for the Ti, Zr, and Nb reagents, initial studies were done using metallocene dichlorides of Ti, Zr, and Nb as pre-catalysts in pinacol couplings. Titanocene dibromide was also evaluated in our pinacol reactions with benzaldehyde although no literature precedents were found for it. Both the acetal and disilyl ether of benzaldehyde were produced depending on the complex employed.

**Table: 2-5: Catalysts evaluated with PhCHO/TMSCl/Mn/THF/ambient temperature**

| Catalyst | Time | product(s):aldehyde[a] | disilyl ether | Acetal |
|---|---|---|---|---|
| $Cp_2TiCl_2$ | 24 h | 1:0 | yes | no |
| $Cp_2TiBr_2$ | 48 h | 1:1 | no | yes |
| $Cp_2ZrCl_2$ | 48 h | 0:1 | no | no |
| $Cp_2NbCl_2$ | 48 h | 1:6 | yes | yes |

[a] ratios determined by G.C. analysis.

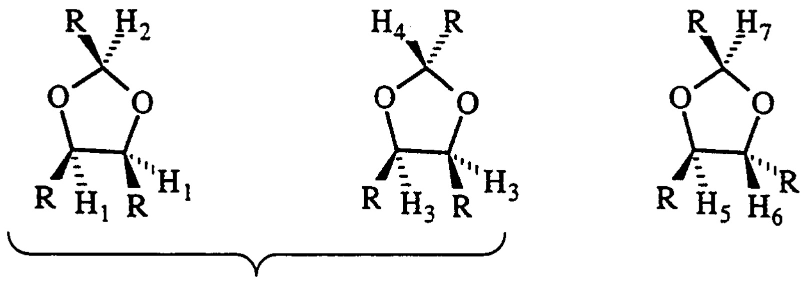
The $Cp_2TiCl_2$ reaction went to completion (aldehyde was completely consumed) within 24 hours and generated only disilyl ether. The *dl:meso* ratio for the disilyl ether in this reaction was 14:1. With the remaining catalysts evaluated, significant amounts of unreacted aldehyde were observed in the G.C. even after three days (Table 2-5).

Zirconocene dichloride was not effective in generating acetal or disilyl ether based on G.C chromatograms. No work-ups were performed with the zirconocene-mediated reactions. The sluggish behavior of this catalyst was attributed to its high reduction potential.[14,15] Manganese was not an effective reductant for the zirconocene dichloride and probably did not reduce it to the desired +3 state.

The $Cp_2NbCl_2$ catalyzed reactions produced disilyl ether; however, the amount of disilyl ether produced was small relative to the amount of acetal generated. The $Cp_2TiBr_2$ catalyzed reaction produced only acetal; no disilyl ether was observed. With both of these reactions, significant amounts of unreacted aldehyde remained after 48 hours. Work-ups and yields were not performed/ calculated with either the niobocene or titanocene (bromide) catalyzed reactions. In these instances where acetal was formed, the *dl* was the major acetal isomer. The *dl:meso* ratio ranged from 2:1 to 3:1 with these two catalysts tested.

The acetal generated in several of these reactions was clearly the *dl* isomer based on NMR splitting patterns. In the *dl* isomer, two of the protons (5 and 6) are non-equivalent and should appear as doublets at 4.95 and 4.98 ppm. Also, proton $H_7$ is seen at 6.41 ppm as a singlet for the *dl* acetal. NMR and GC analysis revealed that at least one of the *meso* isomers was present.

**Figure 2-2: $^1$H NMR splitting pattern for *dl* and *meso* acetals**
R= benzyl



*meso*

$H_1$ = singlet
$H_2$ = singlet

$H_3$ = singlet
$H_4$ = singlet

*dl*

$H_5$ = doublet
$H_6$ = doublet
$H_7$ = singlet

In the *meso* isomer, some of the protons are equivalent and will appear as a singlet. The NMR ring protons for the *meso* isomer (as indicated in Figure 2-2) were singlets observed at 5.54 and 6.21 ppm.

Titanocene dichloride catalyzes the pinacol coupling of benzaldehyde with both a high yield (> 90%) and *dl:meso* (14:1) ratio. While some selectivity was achieved with other catalysts, it was not as great as that achieved with the titanocene dichloride and it was often in the form of the *dl* acetal. Further discussion will be devoted to the acetal formation in chapter five of this dissertation. Since titanocene dichloride yielded the most synthetically useful results, it was chosen as the catalyst for our standard procedure.

*Recycling Agents:* Two recycling agents were investigated in our initial studies using benzaldehyde as the substrate. In later studies with the aliphatic aldehydes, additional recycling agents were evaluated in an attempt to improve both the yield and selectivity (*vide infra*). TMSCl and collidinium chloride were used in our preliminary studies with benzaldehyde. Gansauer was the first to utilize collidinium chloride, and he indicated that this recycling agent actually enhanced the selectivity of the pinacol reaction. The yield for the coupling of benzaldehyde decreased somewhat when collidinium chloride was substituted for the TMSCl (90% to 68%).[16,17] However, in our experiments with collidinium chloride, we observed a slight decrease in *dl* selectivity and a significant decrease in the rate of reaction (Table 2-6).

**Table 2-6: Recycling agents--TMSCl and collidinium chloride**[a]

| Reagent | Product:Aldehyde[b] | dl:meso[b] |
|---|---|---|
| TMSCl | 1:0[c] | 14:1 |
| Collid-HCl | 1:3[d] | 10:1 |

[a] Reaction conditions were PhCHO,Mn,$Cp_2TiCl_2$, THF, ambient temperature, quick addition; [b] based on NMR and or GC; [c] after 24 h; [d] after 6 days.

Based on the results obtained for both of these recycling agents, TMSCl was chosen as the recycling agent for our optimized procedure and was generally employed in subsequent reactions.

*Solvents:* Both organic and aqueous media have been evaluated in our catalytic pinacol reactions. The organic solvents investigated to date include THF, $CH_2Cl_2$, diethyl ether and toluene. The aqueous medium evaluated was a combination of water and THF. In reactions using the four different organic solvents (Table 2-7), it was discovered that only in THF was the pinacol disilyl ether generated in a substantial amount.

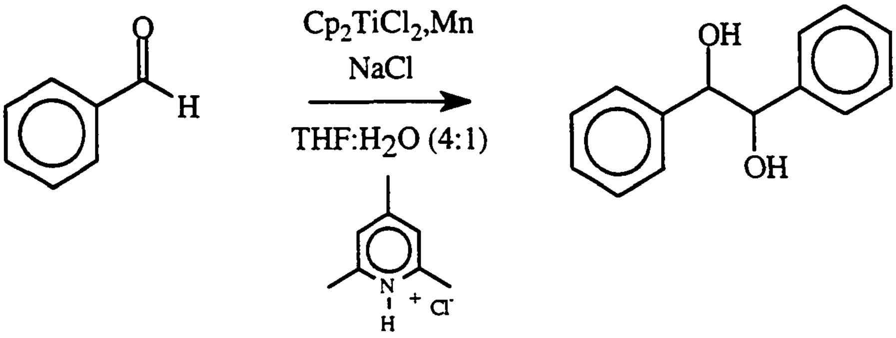
**Table 2-7: Organic solvents in catalytic pinacol couplings**[a]

| solvent | time (hr.) | product:aldehyde |
|---|---|---|
| THF | 24 | 1:0 |
| $CH_2Cl_2$ | 48 | 1:3 |
| toluene | 48 | 1:4 |
| ether | 24 | 1:37 |

[a] Reaction conditions: PhCHO, Mn, TMSCl, $Cp_2TiCl_2$, ambient temperature

An aqueous medium was also employed in some of the attempted catalytic pinacol reactions. Reactions using stoichiometric amounts of titanium trichloride in aqueous media have been reported and were elaborated upon in chapter one.[1,2] Moreover, an aqueous stereoselective pinacol using $[Cp_2TiCl]_2$ in combination with NaCl as an additive was discussed in chapter one as well.[5] Given these precedents, our efforts were focused on performing an aqueous pinacol reaction that was catalytic (Scheme 2-9).

**Scheme 2-9: Aqueous, catalytic pinacol reaction**



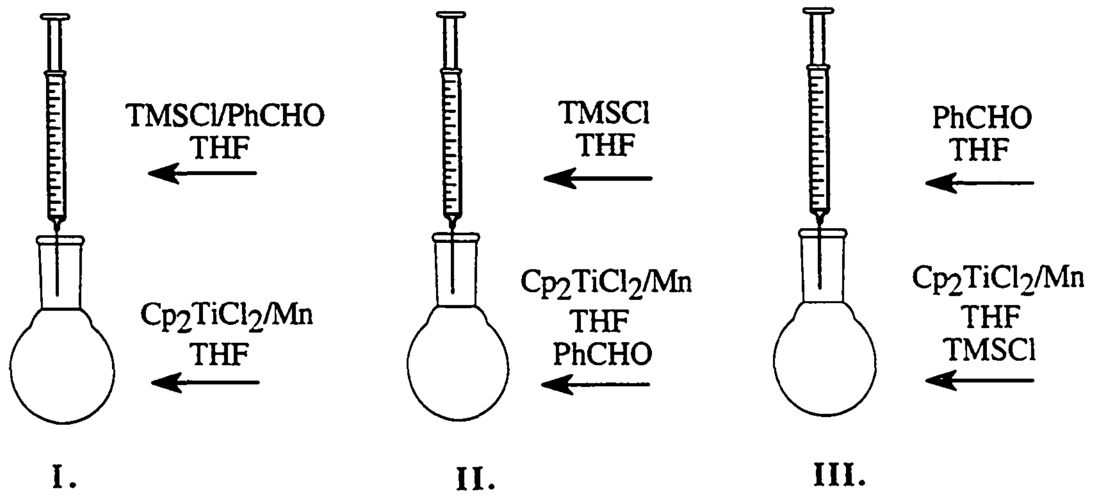
Schwartz employed a THF:$H_2O$ ratio of 4:1 and used NaCl as an additive to enhance pinacol coupling.[5] Both his solvent combination and NaCl additive were adopted for our catalytic system. The recycling agent, collidinium chloride, used by Gansauer was also employed in our aqueous, catalytic system.[16,17] The titanium catalyst and stoichiometric reducing metal used in previous reactions was maintained for this system.

After 20 hours, it was noted that the product:aldehyde ratio (based on G.C.) was 2:1. The reaction was worked up, and the *dl:meso* ratio seen for the hydrobenzoin was 2:1. Several side products were present based on both NMR and GC analysis. Although the selectivity was moderate and the starting material was not consumed, the fact that coupling occurred under aqueous conditions was promising. Subsequent efforts were focused on improving the aqueous catalytic pinacol system through various modes of addition. However, these attempts were unsuccessful. Since further improvements with the aqueous media system were not obtained, additional work was not performed in this particular area.

*Temperature:* Only a few temperatures were evaluated for the pinacol coupling reactions (-78°C, 0°C, and ambient temperature). The -78°C temperature was employed only in an effort to prevent the metal reducing agent (e.g. zinc) from effecting the pinacol coupling in the absence of the metallocene catalyst. In this control reaction, the temperature successfully prevented zinc from coupling benzaldehyde in the absence of catalyst; however, when $Cp_2TiCl_2$ was added, the reaction failed to produce pinacol. In comparing 0°C and ambient temperature, it was hypothesized that at low temperatures the reaction rate would decrease while the selectivity for the *dl* isomer would increase. Based on the hypothesized trimetallic intermediate,[3,6,16-20] the transition state energy to form the *dl* isomer should be lower than that for the *meso* isomer. By lowering the temperature, we hoped to further enhance selectivity for the *dl* isomer. Unfortunately, in the reaction performed at 0°C, the rate decreased dramatically and selectivity for the *dl* isomer did not improve based on G.C. analysis. Reactions performed at room temperature produced the highest yields, and in some cases (*vide infra*) very high selectivity for the *dl* isomer.

*Modes of Addition:* The order in which the reagents were combined was another variable examined while developing the standard/optimal procedure. Both the addition of benzaldehyde and TMSCl were manipulated. Formation of the catalyst did not vary from reaction to reaction. Hence, the reducing metal, manganese, and titanocene dichloride were initially combined in THF under nitrogen. Once the titanocene was in the active +3 form (color change from red to green), the order of additions was evaluated. In one instance, both the benzaldehyde and TMSCl were added quickly (within a few minutes) *via* syringe to the flask containing the active catalyst. This method proved to be the most effective in that fewer side products were generated according to G.C. analysis.

**Figure 2-3: Slow modes of addition**



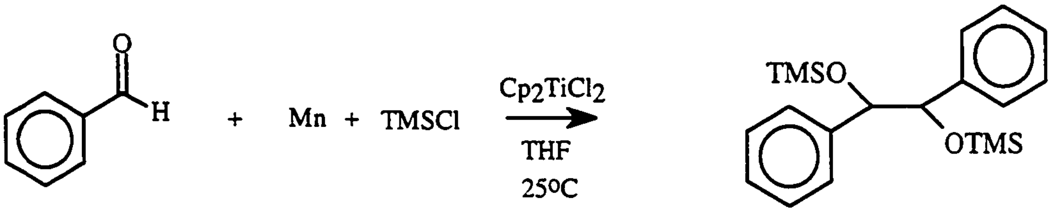
As for the slow additions, three methods were studied. First, the TMSCl and benzaldehyde were combined in THF and slowly added to the active catalyst solution. Second, a TMSCl/THF solution was slowly added to the reaction vessel containing active catalyst and benzaldehyde; and third, a benzaldehyde/THF solution was added slowly to a solution of catalyst and TMSCl. All of these slow additions were performed using syringes and were carried out over a period of several hours.

Diastereoselectivities remained high regardless of the mode of addition (90-95%); however, the yield was affected by the changes in addition. In the three cases in which slow additions were performed, substantial amounts of benzaldehyde were observed in the gas chromatogram after 48 hours. The G.C.'s from the quick addition of TMSCl and benzaldehyde indicated that benzaldehyde had been consumed after 20 to 24 hours.

After evaluating the four possible modes of addition, it was concluded that the rapid addition of both the benzaldehyde and the TMSCl provided the optimal results. Hence, for all future experiments investigating other variables, the recycling agent and carbonyl substrate were added quickly to the titanium +3 catalyst solution.

In summary, six variables were examined when developing an optimal procedure with benzaldehyde.

**Scheme 2-10: Standard or Optimal Procedure**



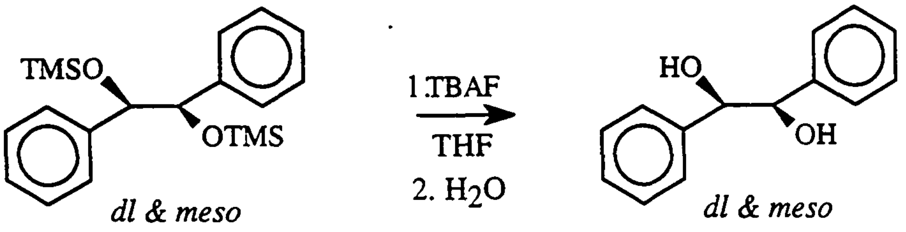
% Yield: > 90
de: 90-95%

The optimal procedure utilizes manganese as the stoichiometric reducing metal, TMSCl as the recycling agent, titanocene dichloride as the catalyst, and THF as the solvent. The other criteria of importance include running the reactions at ambient temperature and using a rapid addition of TMSCl as well as PhCHO to the active catalyst generated from the manganese and titanocene dichloride. The reaction runs for approximately 24 hours. The G.C. chromatograms indicate that aldehyde has been consumed after 24 hours. Next, the crude mixture is filtered, and concentrated to a residue. The residue is triturated with a mixture of petroleum ether/ether and filtered again through Celite. The filtrate is then concentrated to an oil. Flash chromatography is performed using a mixture of petroleum ether and ether to isolate the *dl* and *meso* disilyl ethers. The purified products were analyzed by proton and carbon NMR as well as GC/MS.

*Differentiation of dl and meso isomers*

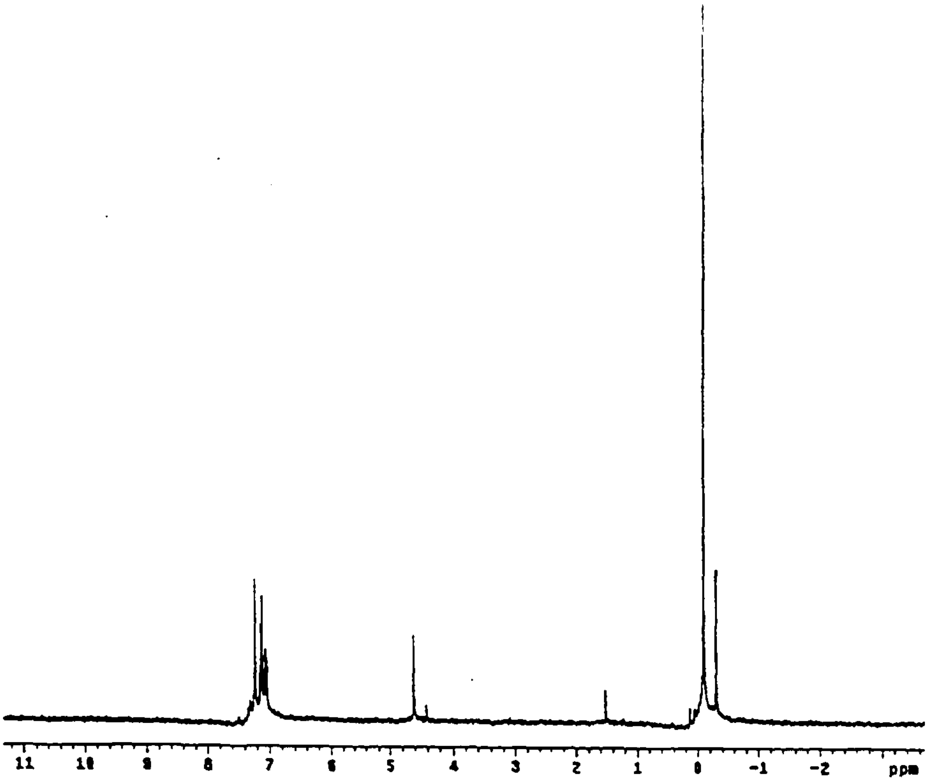
We tentatively concluded that the major isomer obtained in our pinacol reactions was the *dl* isomer while the minor one was the *meso*. This conclusion was based on the work of Gansauer and Nelson who reported the *dl* isomer as the major one when using very similar systems. Additional verification was necessary to conclude that the *dl* isomer was the major product in our system. Unfortunately, spectral data on the isomeric disilyl ethers was not available; however, the $^1$H NMR chemical shifts of the *dl* and *meso* hydrobenzoin were published.[21] The disilyl ether that was isolated from our optimal procedure was therefore desilylated to the diol using TBAF in THF.

**Scheme 2-11: Desilylation of pinacol product**



The NMR chemical shifts of our diol mixture were compared to those reported by Furstner which indicated that our major isomer was in fact the *dl* one and the minor, *meso*.

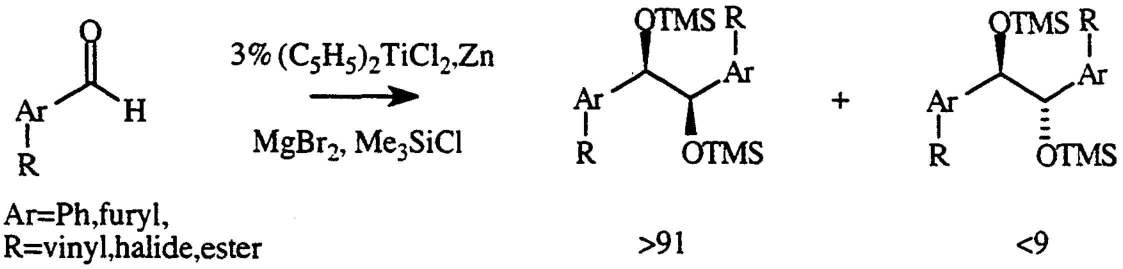
Figure 2-4: $^1$H NMR of *dl* and *meso* 1,2-*bis*(trimethylsiloxy)-1,2-diphenylethane (*dl* isomer $\delta$= 4.63 (s, 2H); meso isomer $\delta$ =4.42 (s, 2H))



### Research endeavors parallel to this dissertation

Numerous papers with research related to ours were published while we were pursuing and developing the pinacol project. In some instances, the same metallocene derivative was utilized. Andreas Gansauer, for example, found that a stereoselective, catalytic pinacol reaction can be achieved with aromatic aldehydes using titanocene dichloride/Zn.[18,20]

**Scheme 2-12: Stereoselective, catalytic system developed by A. Gansauer**

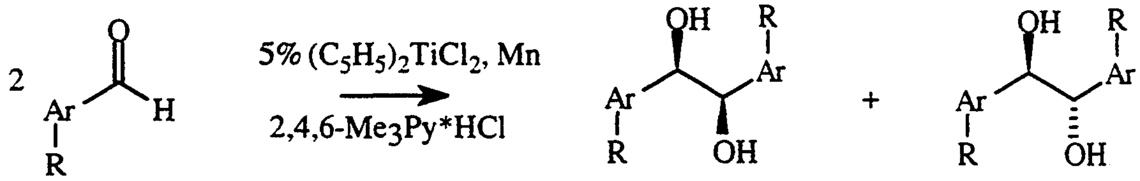


His work differs from ours in that zinc was employed as the reductant, and $MgBr_2$ as an additive. Gansauer indicated that $MgBr_2$ improves the selectivity for the *dl* isomer possibly *via* a tighter dimeric titanium pair by replacing zinc with magnesium.[18] Gansauer utilized a variety of aromatic aldehydes with his system and achieved yields ranging from 80 to 91% and *dl:meso* ratios of approximately 92:8. His work was limited to aromatic aldehydes. As for his procedure, he found that slow addition of a solution of benzaldehyde and TMSCl in THF to the reactive catalyst over two hours improved selectivity.[18] Our results are different than those of Gansauer. The diastereoselectivity did not improve when we utilized a slower mode of addition.

Gansauer also reported a study utilizing titanocene dichloride with a recycling agent other than TMSCl. He evaluated a series of pyridinium chlorides to determine if the pinacol coupling could occur catalytically under buffered protic conditions.[16,17] 2,4,6-

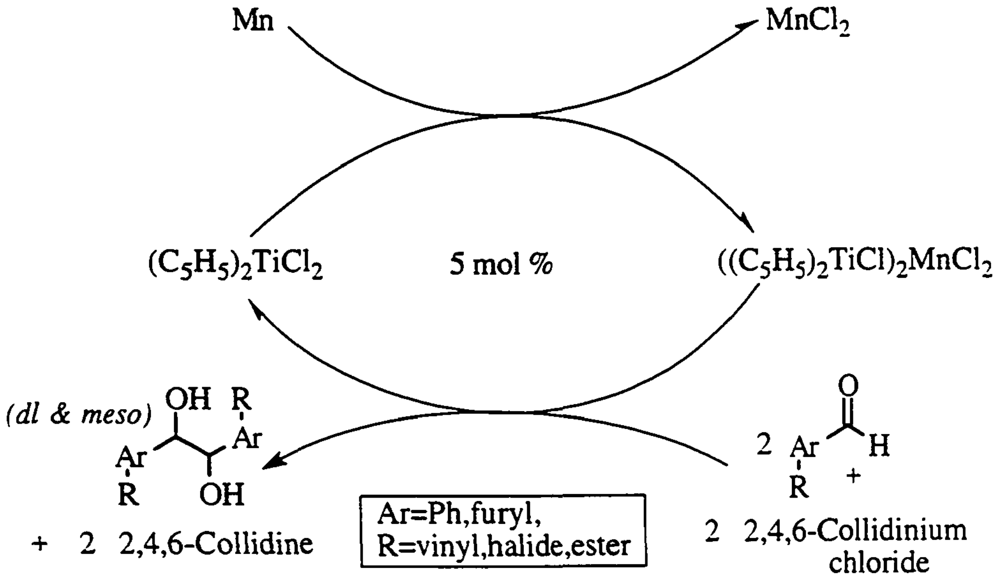
Collidinium chloride gave the optimal results with a 68% yield of hydrobenzoin and a *dl:meso* ratio of 95:5.

**Scheme 2-13: Catalytic pinacol coupling using collidinium chloride as recycling agent**



Gansauer also examined pinacolization of other aromatic aldehydes. Yields ranged from 82 to 91% and *dl:meso* selectivities ranged from 95:5 to 99:1. He described the recycling step as one in which the collidinium chloride protonates the titanium-oxygen bond to produce both the diol product and the original titanocene dichloride. Figure 2-5 illustrates this principle:

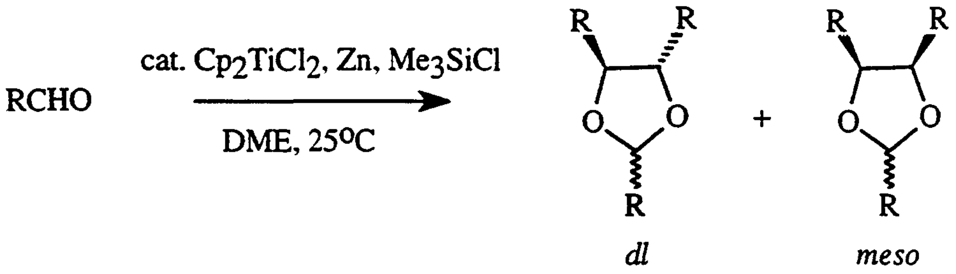
**Figure 2-5: Catalytic cycle using 2,4,6-collidinium chloride**



Gansauer noted that a slight increase in diastereoselectivity was achieved when collidinium chloride was used over TMSCl. Again, our results did not correspond with Gansauer's. We did not find that the collidinium chloride recycling agent produced even a slight improvement in stereoselectivity. We attribute this discrepancy to the slight variations between the Gansauer and Nicholas optimal procedures. Gansauer also reported that the collidinium chloride can be recovered in an aqueous work-up using acid-base extraction.

Hirao and coworkers evaluated aliphatic aldehyde pinacolization using titanocene dichloride and zinc as a stoichiometric reductant.[22]

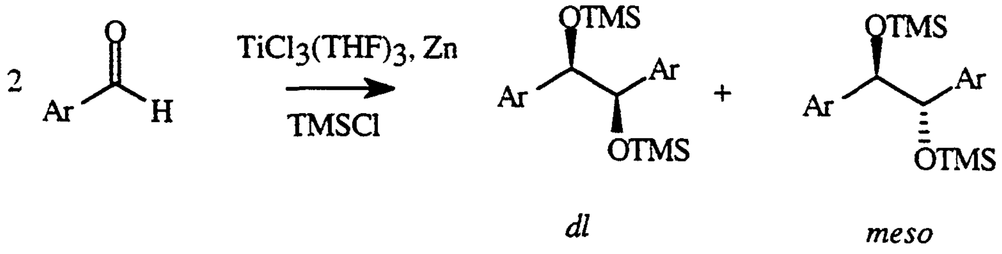
**Scheme 2-14: Catalytic pinacol reaction leading to acetal**



They did not isolate the expected disilyl ether; but instead, the acetal was produced. The solvent media influenced the product formed. In DME, the major product was acetal while in THF, the major product was disilyl ether. The yields ranged from 60 to 88% and *dl:meso* ratios were from 63:37 to 96:4. The more sterically hindered aldehydes produced the higher *dl:meso* ratios.

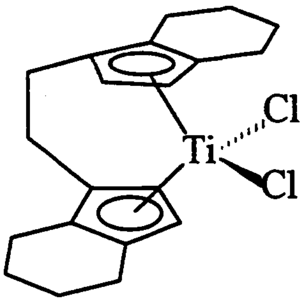
Other titanium-based catalysts have been evaluated for the catalytic pinacol reaction. Nelson and coworkers investigated $TiCl_3(THF)_3$ with zinc and TMSCl for coupling aromatic aldehydes and ketones.[23] Yields ranging from 76 to 95% and *dl:meso* ratios of 60:40 to 83:17 were achieved.

**Scheme 2-15: Pinacol coupling with TiCl$_3$(THF)$_3$ catalyst**



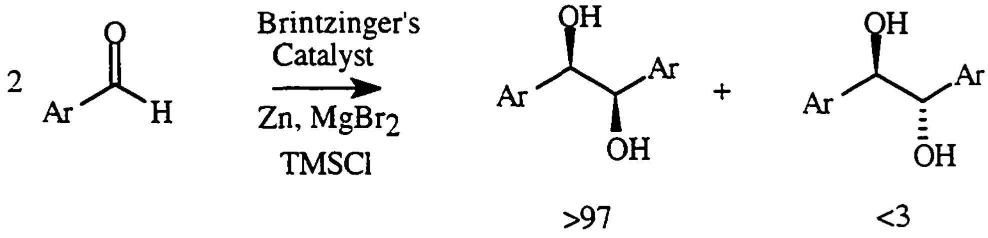
Brintzinger's titanium complex has also been shown to catalyze the pinacol reaction.[19]

**Figure 2-6: Brintzinger's Catalyst**



Pinacolization of aromatic aldehydes were investigated using racemic Brintzinger's catalyst in a procedure developed by Gansauer.

**Scheme 2-16: Pinacol couplings using Brintzinger's catalyst**

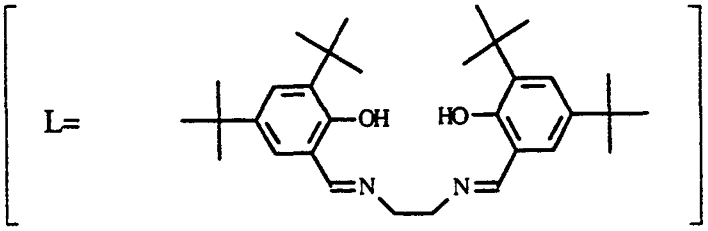


Yields ranged from 79 to 88% and *dl:meso* ratios were approximately 97:3 for all the aldehydes tested.

Titanium-Schiff base complexes have also proven successful at catalyzing pinacol reactions with aromatic aldehydes.[24] The Schiff base was reacted with $TiCl_4(THF)_2$ in acetonitrile. Because of their air and moisture sensitive nature, the catalysts were prepared *in situ*. Bandini studied several ligands; only one will be illustrated:

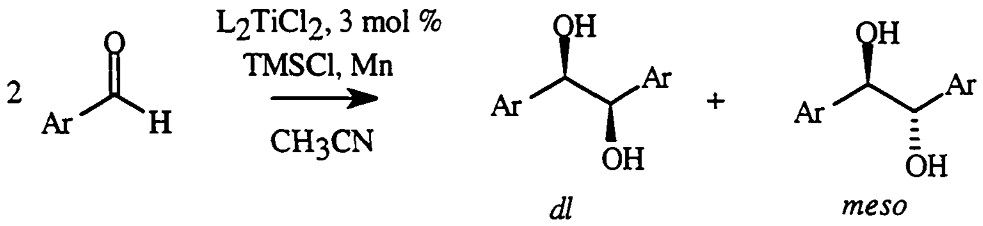
**Scheme 2-17: Synthesis of titanium-schiff base reagent**

$$2L + TiCl_4(THF)_2 \xrightarrow{CH_3CN} L_2TiCl_2$$



Once the titanium-Schiff base complex was generated, the manganese and TMSCl were added. The solution eventually became green-blue which indicated that the titanium had been reduced to the +3 state. At this point, the substrate was added to the reaction vessel.

**Scheme 2-18: Catalytic pinacol using titanium-schiff base catalyst**



The titanium-Schiff base catalysts produced yields from 40 to 83% and *dl:meso* ratios from 52:48 to 99:1.

A number of metals other than titanium-based ones have been employed very recently to catalyze pinacol couplings. $CrCl_3$,[25] $SmI_2$,[26] and a thiolate-bridged diruthenium complex[27] catalyze the pinacol reaction of aromatic aldehydes. In all of these cases, a silyl reagent and a reducing metal were used. While it was clear that these other reductants generated the pinacol, the yields as well as the diastereoselectivities were lower than what was observed with the titanium systems.

In summary, numerous reports that parallel the pinacol synthetic methodology project in the Nicholas laboratory have been published recently. The systems developed by Nelson and Gansauer using $TiCl_3(THF)_3$ and $Cp_2TiCl_2$, respectively, resembled the work in our laboratory the most. It should be emphasized that the systems developed in Nelson and Gansauer's laboratories focused on the coupling of aromatic aldehydes only. Results with aliphatic aldehydes proved to be poor being sluggish and producing very little product. The system developed in the Nicholas laboratory successfully coupled both aromatic and aliphatic aldehydes (*vide infra*).

## Conclusion

A stereoselective, catalytic pinacol reaction was developed based on two fundamental pinacol systems reported previously. First, stereoselective pinacol couplings were known using stoichiometric quantities of titanium reagents. Second, a TMSCl/Zn system could generate the pinacol product and avoid using the usual aqueous work-up employed to replace the metal-oxygen bonds. These precedents laid the foundation for the synthetic methodology project in the Nicholas laboratory.

The initial work focused on developing a standard or optimal procedure that could be applied to a variety of substrates. Six different variables were investigated. Chemical variables included the catalyst, the stoichiometric reducing metal, and the recycling agent. The medium was also studied and included both organic and aqueous options. Both the temperature of the reaction and the modes of addition were also investigated. Through the evaluation of these six variables, an optimal procedure was developed using benzaldehyde as the substrate. The components for the optimal procedure included titanocene dichloride as the catalyst, manganese as the stoichiometric reducing agent, and chlorotrimethylsilane as the recycling agent. The optimal conditions for the remaining three variables included an ambient reaction temperature, THF as solvent, and rapid additions of both the aldehyde and recycling agent to the active catalyst solution. Once the optimal procedure was established using an aromatic aldehyde, work began on applying this procedure to the aliphatic aldehydes. The results achieved using these substrates will be described in chapter three.

## Future Directions

The optimization experiments using benzaldehyde were very successful and allowed us to develop a standard pinacol coupling procedure. However, since numerous research groups are exploring similar metallocene-based systems with aromatic aldehydes, our focus will be directed at substrates other than the aromatic aldehydes. Future work will be directed towards pinacolization of other substrates such as ketones or imines, enantioselective couplings, and mechanistic studies. These additional areas of interest are elaborated upon in chapters 3-5.

## Experimental

### General Methods

All starting materials were commercially obtained. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium and benzophenone. Benzene, toluene, and methylene chloride were distilled under nitrogen from $CaH_2$. Glassware was oven dried (125°C) and flushed with nitrogen before use. Molecular sieves (4 Å) were activated *via* flame drying while under vacuum and were used in all of the optimization reactions with benzaldehyde. Liquids were transferred using syringes, and all solids were manipulated within the dry box.

$^{1}H$ and $^{13}C$ NMR were obtained using a Varian XL-300 or a Varian Unity Inova-400 instrument. All NMR samples were dissolved in $CDCl_3$. A Hewlett Packard 5790A gas chromatograph with a 3m column packed with OV-101 was used for monitoring reactions. GC/MS spectra were obtained on a Hewlett Packard 5985 GC/MS instrument.

Both gravity and flash chromatography techniques were employed. For gravity columns, the silica gel was 60 Å or 70-230 mesh. Flash chromatography utilized silica gel with particle sizes from 32-63 mesh. Petroleum ether, used in combination with diethyl ether for chromatography, was distilled to remove any high boiling impurities.

## Optimization Experiments

### 1. Metal Reducing Agents

### Control reactions using zinc

Zinc (0.017 mol, 1.09 g) was combined with THF (20 ml) in a flask equipped with side arm. The flask was evacuated and flushed with nitrogen. Benzaldehyde (0.0033 mol, 0.34 ml) and TMSCl ($3.4\times10^{-3}$ mol, 0.43 ml) were added to the septum-sealed reaction vessel and the mixture stirred at room temperature. Aliquots were removed and analyzed by G.C. to determine if pinacolization was occurring in the absence of catalyst. The work-up for the aliquots is described in the standard procedure. Several control reactions using zinc metal were performed. Variations employed different particle sizes of zinc and also different temperatures. Three reactions were performed using granular zinc (-30 to +100 mesh) at -78°C, 0°C, and ambient temperature; and, three reactions were performed using zinc powder (-100 mesh) at the three different temperatures.

A substantial amount of disilyl ether product was formed after 1 h in five of the six control reactions. The five control reactions that formed product were aborted. In the control reaction using granular zinc at -78°C, no product had formed after 1 h according to G.C. $Cp_2TiCl_2$ (0.30 mmol, 82 mg) was added to the reaction. Further G.C.'s indicated that product was still not generated after the addition of the titanium catalyst.

### Control and Catalyst reactions using Sn, Fe, and Al

The metal (0.05 mol; Sn: 5.9 g or Fe: 2.8 g or Al: 1.4 g) was placed in a flask equipped with side arm under nitrogen. Distilled THF (20 ml) was added to this flask. Both benzaldehyde ($3.3x10^{-3}$ mol, 0.34 ml) and TMSCl ($3.4x10^{-3}$ mol, 0.43 ml) were added to the reaction flask by syringe. The mixture was stirred for 4 h at ambient temperature. Aliquots were removed after 4 h and analyzed by G.C. (described in standard procedure). Disilyl ether was not detected for any of the reactions using these metals. $Cp_2TiCl_2$ ($3.0x10^{-4}$ mol, 82 mg) was added to the control reaction. G.C.'s of aliquots taken after 24 h still showed no product formation.

### Control and catalyst reactions using manganese and magnesium

The metal (1.2 mmol, Mn: 66 mg or Mg: 29 mg) was placed in a flask equipped with side arm under nitrogen. Distilled THF (20 ml) was added to the vessel. TMSCl (2.2 mmol, 0.28 ml) and benzaldehyde (2.0 mmol, 0.20 ml) were added by syringe. The reactions were stirred for several hours. Aliquots were removed and examined by G.C. No disilyl ether was observed at this point (24 h). The $Cp_2TiCl_2$ (0.2 mmol, 50 mg) was added to each reaction vessel and the reactions were monitored by G.C. After approximately 24 h, the aldehyde was consumed. Work-up is described in the standard procedure. NMR data indicated that higher yields and selectivities could be obtained with manganese compared to magnesium.

Magnesium: 70% yield; *dl:meso*: 95:5

Manganese: >90% yield; *dl:meso*: 97:3

## 2. Catalyst

Manganese (1.2 mmol, 66 mg) and the metallocene complex ( 0.20 mmol,  mg*) were combined with 20 ml of distilled THF under nitrogen. The mixture was stirred at ambient temperature for 15 min. Next, TMSCl (2.2 mmol, 0.28 ml) was added quickly by syringe followed by the addition of benzaldehyde (2.0 mmol, 0.20 ml). The reaction stirred from 1 to 3 days depending on the catalyst utilized, and the reaction was monitored by G.C. A description of the procedure for removing aliquots and the final work-up utilized is provided later in the standard procedure. Acetal (2,4,5-triphenyl-1,3-dioxolane) was formed in some of these reactions.

*$Cp_2TiCl_2$: 50 mg; $Cp_2TiBr_2$: 68 mg; $Cp_2ZrCl_2$ 58 mg; $Cp_2NbCl_2$: 30 mg; .

*2,4,5-triphenyl-1,3-dioxolane*

*$^1H$ NMR ($CDCl_3$) $\delta$ dl* isomer: 4.95 (d, J=8.1 Hz, 1H), 4.98 (d, J= 7.8 Hz, 1H), 6.41 (s, 1H), 7.25-7.80 (m, 15H); *meso*: 5.54 (s, 2H), 6.21 (s, 1H), 7.25-7.80 (m, 15H); *GC/MS 12ev EI* m/e (intensity): 196 ($M^+$-106, 100), 180 ($M^+$-122, 2.3), 103 ($M^+$-199, 0.2)

## 3. Recycling Agents

The recycling agents used include TMSCl and collidinium chloride. Gansauer's preparation of collidinium chloride was utilized.[16] Procedures for testing recycling agents were fairly similar. Amounts of reagents used for the collidinium chloride reaction were different from the usual combination employed: and, the general procedure was modeled after one presented by Gansauer.[16]

### Pinacolization using collidinium chloride as recycling agent

For the collidinium chloride reaction, manganese (2.00 mmol, 110 mg) and $Cp_2TiCl_2$ (0.15 mmol, 37 mg) were combined with 15 ml of THF in a side arm flask under nitrogen. This solution stirred at an ambient temperature for 15 min. The collidinium chloride was then introduced into the reaction flask and allowed to stir for an additional 10 min. The benzaldehyde (2.0 mmol, 0.20 ml) in 10 ml of THF was added over a period of 2 h to the reaction vessel. The mixture stirred for 6 days and was monitored by the G.C. Finally, the mixture was combined with diethyl ether (10 ml) and aqueous HCl (10 ml). The organic layer was separated and washed with 1M HCl (10 ml), saturated $NaHCO_3$ (10 ml), and brine (10 ml). The organic layer was then dried over $MgSO_4$ and concentrated.

### Pinacolization using TMSCl as recycling agent

The reaction with TMSCl employed the usual ratios of reagents. The catalyst was generated by combining Mn (1.2 mmol, 66 mg) and $Cp_2TiCl_2$ (0.20 mmol, 50 mg) with 20 ml of THF under nitrogen at ambient temperature. TMSCl (2.2 mmol, 0.28 ml) was added followed by the benzaldehyde (2.0 mmol, 0.20 ml). The reaction was monitored by G.C. and worked-up ( see model procedure for description of aliquot removal and work-up) after one day.

## 4. Solvents

### Organic Solvent

Four different solvents were evaluated (THF, $CH_2Cl_2$, toluene, diethyl ether). For all four reactions, magnesium (1.2 mmol, 29 mg) was combined with $Cp_2TiCl_2$ (0.20 mmol, 50 mg) and 20 ml of the particular distilled solvent. This solution was stirred for 15 min under nitrogen at room temperature. TMSCl (2.2 mmol, 0.28 ml) was added using a syringe followed by benzaldehyde (2.0 mmol, 0.20 ml). The reactions were monitored by G.C. The aliquot removal and work-up method are described in the standard procedure.

### Aqueous media

Manganese (2.0 mmol, 110 mg), NaCl (12 mmol, 0.70g), and $Cp_2TiCl_2$ (0.20 mmol, 50 mg) were combined in a flask with side arm under nitrogen. A THF:water mixture (4:1, 20 ml total) was added to the flask, and the contents of the flask were stirred for 15 min. The solution initially was orange but eventually became yellow. The collidinium chloride (3.0 mmol, 0.47g) was added next. Within 5 min, the solution became light green. Next, benzaldehyde was added dropwise over a few min. The mixture became blue within ten min. The reaction was monitored by G.C. and indicated the formation of the pinacol product along with numerous side products. After 24 h, the reaction mixture was quenched with 1M HCl (10 ml). The aqueous layer was extracted several times with ether (3 x 10 ml), and the combined ether extracts were washed with 1M HCl (10 ml), saturated $NaHCO_3$ (10 ml), and brine (10 ml). Next, the combined organics were dried over $Na_2SO_4$ and concentrated (63 mg). The NMR and G.C. analysis indicated that diol had formed with a *dl:meso* ratio of 2:1. Substantial unreacted aldehyde was seen along with a number of unknown compounds in the NMR.

## 5. Temperature

Reactions using benzaldehyde (2.0 mmol, 0.20 ml) as the substrate, TMSCl (2.2 mmol, 0.28 ml) as the recycling agent, and an active catalyst generated by manganese (1.2 mmol, 66 mg) and $Cp_2TiCl_2$ (0.20 mmol, 50 mg) in THF, were performed at both 0°C and ambient temperature. The reactions were kept under nitrogen and were monitored by G.C. The procedures for removing aliquots and the work-up are described in the standard procedure.

## 6. Mode of Addition

Four modes of addition were investigated. In all four, the active catalyst was generated in the same way. The manganese (1.2 mmol, 66 mg) and $Cp_2TiCl_2$ (0.20 mmol, 50 mg) were combined under nitrogen in a side arm flask. Distilled THF (20 ml) was added to the mixture and it was allowed to stir at room temperature until a color change from red to green occurred. Once the color change occurred, the various methods for adding TMSCl (2.2 mmol, 0.28 ml) and benzaldehyde (2.0 mmol, 0.20 ml) were performed.

*I. Quick addition:* The TMSCl was added quickly (3 s) followed by the benzaldehyde (3 s) a few minutes later. Syringes were used to make these transfers.

*II. Slow addition of TMSCl:* The benzaldehyde was added to the reaction flask containing the active titanium catalyst. TMSCl was combined with 10 ml of THF and added to the reaction vessel over a period of 2 h.

*III. Slow addition of benzaldehyde:* The TMSCl was added to the reaction vessel. The benzaldehyde was combined with 10 ml of THF and slowly added to the reaction flask over a period of 2 h.

*IV. Slow addition of benzaldehyde and TMSCl:* Both TMSCl and benzaldehyde were combined in 10 ml of THF and added over a period of 2 h to the reaction flask containing the active titanium catalyst.

Reactions were stirred from 24-48 h and were all monitored by G.C. The work-up procedure is elaborated upon in the model procedure described later on in this section.

## Standard Procedure for Disilyl Ether Preparation *via* Pinacol Coupling

To a side arm round bottom flask was added activated 4Å molecular sieves (one spatula), titanocene dichloride (0.20 mmol, 50 mg), and manganese (50 mesh, 1.2 mmol, 66 mg) under nitrogen. Distilled THF (20 ml) was added and the mixture was stirred for 15 minutes while changing from red to green. Trimethylsilylchloride (2.2 mmol, 0.28 ml) was added using a syringe followed by the aldehyde (2.0 mmol, 0.20 ml) and the mixture was stirred at 25 °C for 24 h. Aliquots (approx. 0.5 ml) were removed while the reaction was in progress. The aliquots were filtered through Celite, dried over a stream of nitrogen, triturated with 4:1 petroleum ether:ether, and filtered through celite again. Next, the aliquots were injected onto the G.C. to monitor the reaction progress. Once the GC analysis indicated that all the aldehyde had been consumed, the reaction was worked-up. The volatiles were removed by rotary evaporation, the residue was triturated with 4:1 petroleum ether/ether, and the washings filtered through Celite. Concentration of the filtrate produced the crude products as orange or yellow oils. Further purification was accomplished by flash chromatography over silica gel using petroleum ether/ether as eluant providing the pinacol-*bis*-silyl ethers as colorless oils. The products were characterized by $^1H$ and $^{13}C$ NMR and mass spectrometry.

*1,2-bis(trimethylsiloxy)-1,2-diphenylethane*

GC & NMR purity ≥ 93%; yield: 73%; *dl:meso* : 14:1; *$^1H$ NMR*: ($CDCl_3$) $\delta$ minor isomer: -0.29 (s, 18H), 4.42 (s, 2H), 7.00-7.18 (m, 10H); major isomer: -0.09 (s, 18H), 4.63 (s, 2H), 7.20, 7.31 (m, 10H); *$^{13}$C NMR*: (CDCl3) δ maj + min: -0.50,-0.05. 79.38, 79.76, 126.85, 127.12, 127.34, 141.80, 143.10; *GCMS* (12 ev EI) m/e (intensity): 179.1 (M$^{+}$-179.1, 100) for both GC peaks

### Desilylation of 1,2-bis(trimethylsiloxy)-1,2-diphenylethane

The *bis*-silylether (0.342 mmol, 116 mg) was combined with 10 ml of THF in a round bottom flask equipped with a water condensor. This solution stirred for a few minutes until the *bis*-silyl ether had dissolved. Next, tetrabutylammonium fluoride, TBAF, (1.0 M in THF, 0.30 ml; excess) was added using a syringe. The solution became dark brown after this addition. The mixture was refluxed for 4 h. Next, the solution was cooled to ambient temperature and was quenched with 10 ml of water. The aqueous layer was extracted three times with diethyl ether. The organic layers were combined and dried over $Na_2SO_4$ and concentrated. The crude material was passed over a silica gel pipet column using ether as the eluent.

*dl and meso hydrobenzoin*

Crude yield: 55.3%; Purified yield: 20.2%; *$^{1}$H NMR* ($CDCl_3$) δ maj: 2.81 (broad s, 2H), 4.70 (s, 2H), 7.10-7.45 (m, 10H); min: 4.80 (s, 2H), 7.10-7.45 (m, 10H)

Published data:[21] *$^{1}$H NMR* ($CDCl_3$) δ: *dl* isomer 4.70 (s, 2H); *meso* isomer: 4.80 (s, 2H).

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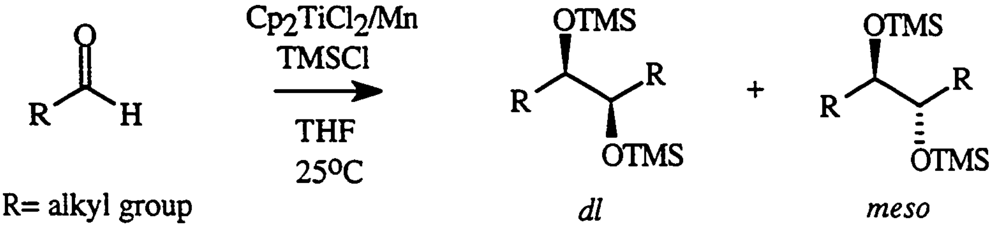
# CHAPTER 3

# PINACOLIZATION OF ALIPHATIC ALDEHYDES AND OPTIMIZATION EXPERIMENTS

## Introduction and Background

An optimal procedure for a stereoselective, catalytic pinacol reaction was developed using benzaldehyde as the substrate. These initial results with benzaldehyde were quite promising; therefore, additional substrates were evaluated with our pinacolization method. While these optimization studies were being investigated in our laboratory, other stereoselective, catalytic pinacol systems for aromatic aldehydes were published.[1-3] Because of this parallel research, further work with aromatic aldehydes would have been repetitive and was therefore not explored. As for coupling aliphatic aldehydes, little work had been reported.

**Scheme 3-1: Coupling of aliphatic aldehydes**



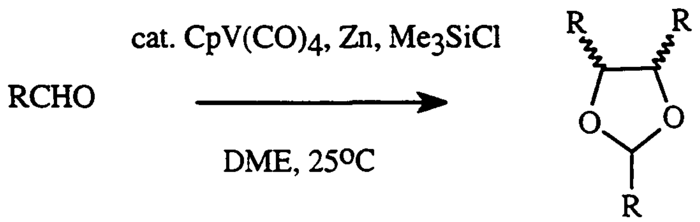
Stereoselective couplings of aliphatic aldehydes has been achieved with stoichiometric amounts of metal reductants (i.e.: $NbCl_3$-DME);[4,5] however, no systems using catalytic amounts of metallocenes had been published when we began our investigation with the aliphatic substrates. Since considerable work had been performed with aromatic aldehydes and work with aliphatic aldehydes was limited, the optimized procedure was applied to a variety of aliphatic aldehydes.

*Electronic and steric features*

The reduction potentials for aromatic and aliphatic substrates are quite different. For the reduction of aromatic aldehydes and ketones to their respective radical anions, the potentials are from -1.8 to -2.0 V vs. SCE in DMF. Reduction of aliphatic ketones or aldehydes to radical anions requires a potential from -2.2 to -2.8 V vs. SCE in DMF.[6] Given the electrochemical data, reduction of aliphatic substrates is thus more difficult than reduction of aromatic ones. In most of the catalytic pinacol couplings cited in chapter two, aromatic aldehydes were the primary substrates utilized while aliphatic aldehydes received little attention.[1-3,7-12] When aliphatic aldehydes had been investigated, yields were considerably lower than with aromatic aldehydes.[13-15]

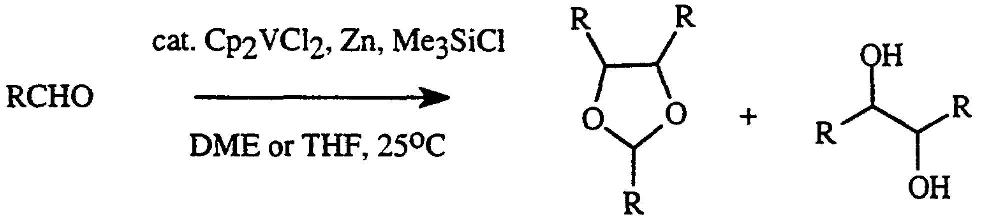
While our study was in progress, vanadium complexes were explored as pinacolization catalysts with aliphatic aldehydes. In Hirao's initial work, he found that a $CpV(CO)_4/Zn$ system coupled aliphatic aldehydes to produce the acetal pinacol.[15]

**Scheme 3-2: Coupling of aliphatic aldehydes using vanadium catalysts**



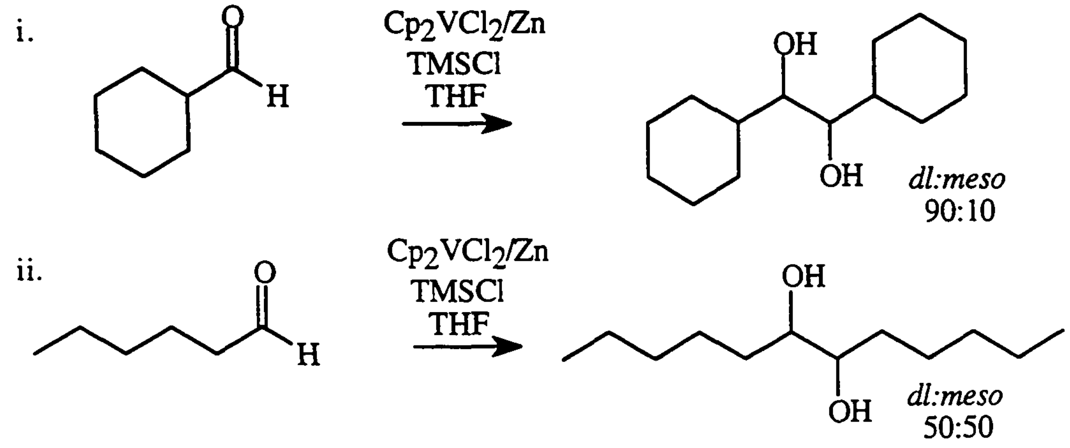
Although the system was catalytic, no diastereoselectivity (50:50 *dl:meso*) was achieved. Further investigations by Hirao utilized $Cp_2VCl_2$ as catalyst and produced some stereoselectivity.[14] Also, it was discovered that formation of the two products could be controlled by the solvent utilized.

**Scheme 3-3: $Cp_2VCl_2$ catalyzed pinacol reaction of aliphatic aldehydes**



With DME as solvent, the acetal was observed (80% yield) in a *dl:meso* ratio of 88:12. When THF was utilized, the diol was formed in 74% yield with a *dl:meso* ratio of 70:30. In the vanadium-catalyzed reactions, the diastereoselectivity obtained with aliphatic aldehydes was less than that obtained with aromatic aldehydes.[14] This result can be attributed to the flexible nature of the alkyl group present in the aliphatic aldehyde. Additional aliphatic substrates evaluated by Hirao indicate that the steric nature of the aldehyde influences diastereoselectivity.

**Scheme 3-4: Coupling of aliphatic aldehydes of varying steric bulk**



For instance, Hirao found that the *dl:meso* ratio for coupling cyclohexanecarboxaldehyde was 90:10 while the ratio for n-hexanal was 50:50.[14]

## Results and Discussion

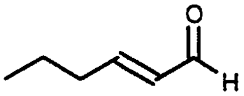
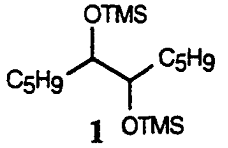
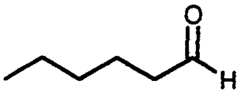
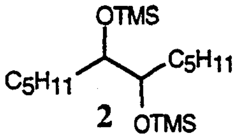
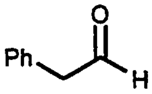
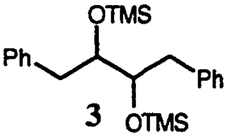
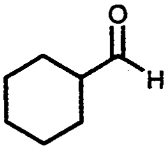
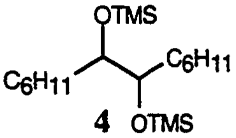
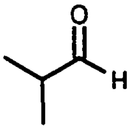
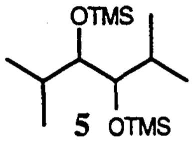
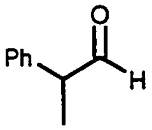
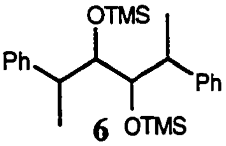
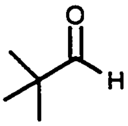
### *Standard or optimized procedure for aliphatic aldehydes*

The standard procedure developed with benzaldehyde ($Cp_2TiCl_2$/ Mn/ TMSCl/ THF/ ambient temperature) was applied to a number of aliphatic aldehydes. It was discovered that coupling occurred with the majority of the aldehydes (Table 3-1). Reactions ran from 18 to 48 hours and produced good yields. As mentioned in chapter two, the reaction time for benzaldehyde coupling was approximately 24 hours. Reactions were usually slower with the aliphatic substrates, and diastereoselectivity was somewhat less for aliphatic aldehydes as well. The highest *dl:meso* ratio for the aliphatic substrates was 3:1 while the *dl:meso* ratio achieved with benzaldehyde was 13:1.

The less hindered aldehydes like 2-hexenal and hexanal required the shortest reaction period of approximately 18 hours. As the aldehydes became more hindered, the reaction times increased. Both cyclohexanecarboxaldehyde and isobutyraldehyde required 48 hours for the reaction to go to completion. The most sterically hindered aldehyde, pivaldehyde, showed no signs of pinacolization even after 48 hours. From these observations, it was apparent that as the aldehydes became more sterically hindered, the reaction rate decreased.

The yields were good for the majority of the aldehydes tested. With the exception of 2-hexenal, as the aldehydes became more hindered, the yields decreased. Some of the less hindered aldehydes like phenylacetaldehyde and hexanal produced higher yields (93% and 80% respectively) than the more hindered 2-phenylpropionaldehyde and isobutyraldehyde substrates (47% and 60% respectively).

**Table 3-1: Aliphatic aldehyde pinacolization by Mn/$Cp_2TiCl_2$/TMSCl**

| Aldehyde | Product | Time (hr) | Yield (%)[a] | Diastereomer ratio |
|---|---|---|---|---|
|  |  **1** | 18 | 45 | 2:1 |
|  |  **2** | 18 | 80 | 1.5:1 |
|  |  **3** | 40 | 93 | 3:1 |
|  |  **4** | 48 | 81 | 2:1 |
|  |  **5** | 48 | 60 | 2.5:1 |
|  |  **6** | 72 | 47 | 2:1:1:1 |
|  | --- | 48 | no rxn. | --- |

[a]Aldehyde completely consumed based on G.C. of crude product; yields based on amount of product present after flash chromatography

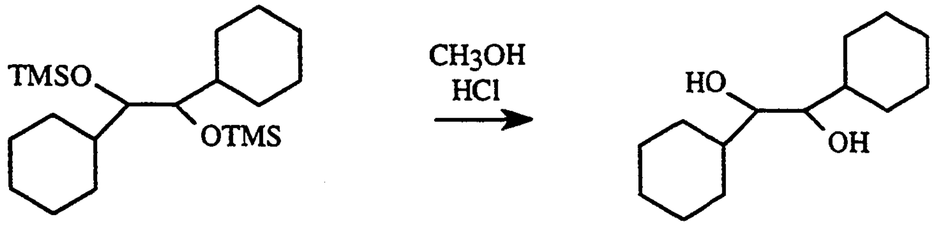
The low yield with 2-hexenal, an α,β-unsaturated aldehyde, could be attributed to the unit of unsaturation that may have produced additional side products through alternative couplings, reduction in a 1,2- or 1,4- fashion or polymerization. However, from GC/MS data, only the desired head to head coupling was observed. There was no indication of head to tail coupling or 1,2 and 1,4-reduction. Polymerization could not be detected by GC/MS and therefore cannot be entirely eliminated from the range of possible side products.

The diastereoselectivities for the pinacolization of aliphatic aldehydes were moderate compared to those obtained with benzaldehyde. Selectivities ranged from 3:1 to 1.5:1 (*dl:meso*). The more sterically hindered aldehydes tended to produce slightly higher *dl:meso* ratios. For instance, cyclohexanecarboxaldehyde (2:1), isobutyraldehyde (2.5:1), and phenylacetaldehyde (3:1) all produced higher *dl:meso* ratios. n-Hexanal, the least hindered aldehyde, produced only a slight *dl:meso* ratio of 1.5:1, and this lower selectivity was attributed to the flexible nature of the alkyl group. 2-Hexenal was also one of the less hindered aldehydes investigated but generated a *dl:meso* ratio (2:1) comparable with cyclohexanecarboxaldehyde. It was hypothesized that the unsaturation within 2-hexenal contributed to the improved selectivity by providing some rigidity relative to the saturated hexanal substrate.

With the majority of aldehydes studied, only two isomers (*dl* and *meso*) were possible. The primary modes of analysis included proton and carbon NMR as well as GC/MS. The *dl:meso* ratio for each reaction was determined from the ratio of *dl:meso* methine protons (approx. 3.3-4.0 ppm) in the proton NMR. The methine protons had varying splitting patterns depending on the number of protons adjacent to them. Also of assistance in determining this ratio was the resonances for the *dl* and *meso* trimethylsilyl groups in the proton NMR. Mass spectrometry also provided some assistance but no molecular ions were observed even using 12 eV ionization. In the majority of pinacolizations with aliphatic aldehydes, the base peak was half the molecular weight of the molecule. In other words, the pinacol products fragmented in half very readily.

When distinguishing the *dl* and *meso* isomers for the aliphatic aldehydes, we suspected that the major isomer isolated in each of the pinacol reactions was *dl* based on the papers published by Gansauer[1] and Nelson.[3] Additional evidence was necessary to confirm this. Since limited physical data existed for these disilyl ethers, it was necessary to desilylate at least one product to its corresponding diol. Desilylation was carried out on 1,2-*bis*(trimethylsiloxy)-1,2-dicyclohexylethane 4 using $CH_3OH$ and HCl which yielded a mixture of the *dl* and *meso* 1,2-dicyclohexyl-1,2-ethandiol 7.[3]

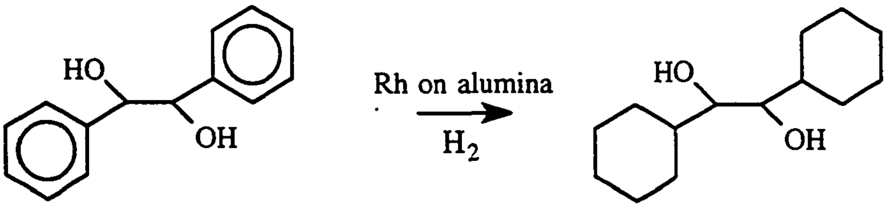
**Scheme 3-5: Desilylation reaction**



4 7

Two sources of data were used to distinguish the chemical shifts of the *dl* and *meso* diols. First, commercially available samples of both racemic (*dl*) hydrobenzoin and *meso* hydrobenzoin were each hydrogenated using rhodium on alumina to the respective aliphatic diol.[16]

**Scheme 3-6: Reduction of *dl* and *meso* hydrobenzoin**



| hydrobenzoin | | 1,2-dicyclohexyl-1,2-ethanediol |
|---|---|---|
| *dl* | → | *dl* |
| *meso* | → | *meso* |

Both the *dl* and *meso* forms of 1,2-dicyclohexyl-1,2-ethanediol were isolated and analyzed individually. The $^1H$ NMR data obtained for each compound helped clarify which resonances corresponded to the *dl* isomer and which were from the *meso* in our mixture.

**Table 3-2: $^1H$ NMR resonances for *dl* and *meso* 1,2-dicyclohexyl-1,2-ethanediol[a]**

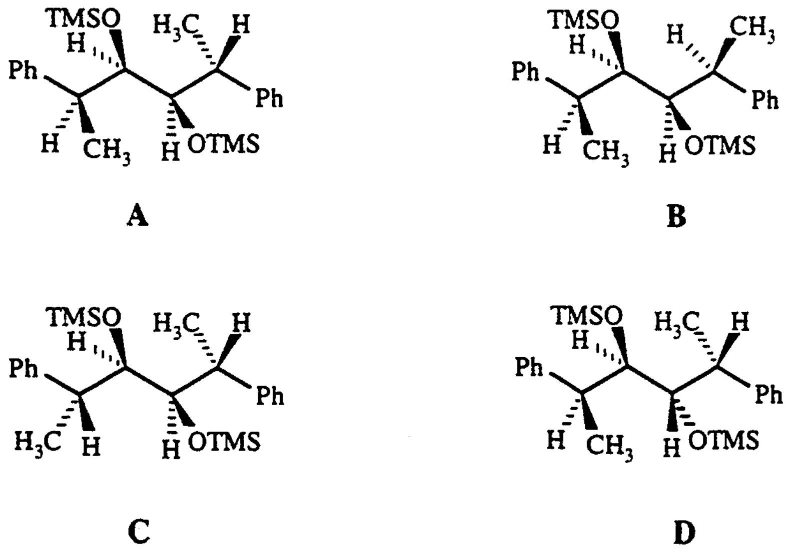
| **authentic *dl* diol[b]** | **authentic *meso* diol[b]** | **rxn mixture major** | **rxn mixture minor** |
|---|---|---|---|
| 3.32 | 3.42 | 3.33 | 3.42 |

[a] units in ppm; [b] data taken from generated authentic samples as well as data reported by Kagan;

From these results, it was clear that the major isomer generated was indeed the *dl.* Further evidence supported this conclusion. Kagan published $^1H$ NMR spectral data that distinguished the *dl* and *meso* isomers of 1,2-dicyclohexyl-1,2-ethanediol.[17] From both the authentic samples of aliphatic diol generated in the lab and the data reported by Kagan, it was concluded that the major isomer obtained from cyclohexanecarboxaldehyde was *dl* . The discovery that the *dl* isomer predominated in the coupling of cyclohexanecarboxaldehyde led us to conclude that the major isomers for the other aliphatic aldehydes were also *dl* .

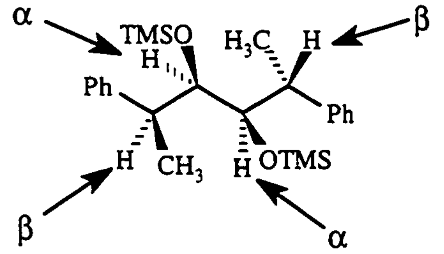
Unlike the other aliphatic aldehydes, 2-phenylpropionaldehyde, after pinacolization, could generate up to four diastereomers because it possessed a stereocenter before the reaction took place. Flash chromatography was used to purify this pinacol product; and based on several fractions, all four isomers appeared to be present in a 2:1:1:1 ratio. Some distinction was made through $^1H$ NMR.

**Figure 3-1: Isomers for 2-phenylpropionaldehyde**



Each stereoisomer theoretically possesses different $^1H$ NMR chemical shifts. Depending on the environment, the protons alpha to the trimethylsiloxy- group contributed a variable number of resonances and sometimes different splitting patterns.

**Figure 3-2: Alpha protons in stereoisomers**



Stereoisomers <u>A-C</u> represent *dl* isomers. In compound <u>A</u>, no element of symmetry is present. Therefore, the α-protons should each appear as a doublet of doublets. Stereoisomers <u>B</u> and <u>C</u> each possesses a $C_2$ axis which should make the two α-protons of a given isomer equivalent, and appear as a doublet. Isomer <u>D</u> represents a *meso* compound which possesses a plane of symmetry; the two α–protons in isomer **D** should appear as a doublet.

The chemical shifts for each isomer were determined based on several fractions taken during flash chromatography (Table 3-3). Most of the fractions taken during chromatography contained at least two of the possible isomers. In order to make some conclusions, the $^1$H NMR spectrum for each fraction was examined independently and in combination with the $^1$H NMR data from other fractions.

**Table 3-3: $^1$H NMR chemical shifts for 6**

| Isomer | β-proton | α-proton |
|---|---|---|
| 1 | 2.53 (m) | 3.52 (d) |
| 2 | 2.88 (m) | 3.64 (d) |
| 3 | 2.99 (m) | 3.74 (d) |
| 4 | 3.11 (m) | 3.82 (d) |

Isomer **2** from Table 3-3 was the major isomer based on the crude NMR. Moreover, it was the primary isomer isolated in one of the fractions and was thus easily interpreted. The peak at 3.64 was a doublet and therefore represents either isomer **B**, **C**, or **D** from Figure 3-1. Isomer **3** (Table 3-3) was found in combination with some of the other products; it possessed a doublet at 3.74 and must represent **B**, **C**, or **D** in Figure 3-1.

One fraction contained what was thought to be primarily isomers **1** and **4** in a 1:1 ratio and small amounts of the other isomers. Isomers **1** and **4** were observed in other fractions as well and were always seen in equal amounts. Because of the constant ratio of **1** and **4** found in different fractions, it was hypothesized that the peaks labeled for isomers **1** and **4** actually represented only one isomer. In this respect, the broad doublets at 3.52 and 3.82 each represented the doublets of doublets expected for isomer **A** (Figure 3-1). If this hypothesis is correct, the ratio of products from the coupling of 2-

phenylpropionaldehyde is not 2:1:1:1 (**A-D**) as listed in Table 3-1, but 2:2:1. In the latter ratio, it is believed that only three isomers (**A** and two of the other ones (**B**, **C**, or **D**)) were actually formed.

Some discrepancies are also present in the interpretation suggesting the presence of all four isomers. While the data in Table 3-3 assigns peaks for all four isomers, it does not account for the doublets of doublets expected with isomer **A**. In all spectra analyzed, only doublets are observed in the 3.5 to 4.0 region. Although some distinction could be made by NMR, it was not complete since some of the isomers were expected to have similar splitting patterns. Chromatography was helpful in that it produced fractions containing one to two isomers. Generalizations could be made about isomers possessing doublets around 3.5. Some data appeared to represent isomer **A**. It was difficult to conclude whether the peaks listed as isomers **1** and **4** represented one isomer or two. At this time, only a partial analysis of the results from coupling 2-phenylpropionaldehyde is possible.

Several aliphatic aldehydes were shown to undergo catalytic pinacol coupling using the standard procedure that was originally developed with benzaldehyde. Yields were good ranging from 45 to 93%, and selectivities were moderate, ranging from 1.5:1 to 3:1 (*dl:meso*). Our results obtained with the catalytic pinacolization of aliphatic substrates were published recently in *Synthetic Communications*.[18] Moreover, while the initial findings with aliphatic aldehydes were encouraging, opportunities for improved rates and stereoselectivities led us to evaluate other variables that might affect and further improve the efficiency of coupling aliphatic aldehydes.

### *Optimization Experiments:*

Several variables were examined in the pinacol couplings of aliphatic aldehydes to improve both yields and diastereoselectivities. Reducing metals, recycling agents, additives, and catalysts were altered with a few of the aliphatic aldehydes. The majority of the variations were performed using cyclohexanecarboxaldehyde as a test substrate. A few experiments utilized isobutyraldehyde and hexanal.

*Reducing Metals:* The standard procedure ($Cp_2TiCl_2$/Mn/TMSCl/THF) developed with benzaldehyde was successfully applied to several aliphatic aldehydes, but the yields were lower and the reaction times were longer. One hypothesis for the poorer results with aliphatic aldehydes is that reduction of aliphatic aldehydes relative to aromatic aldehydes is more difficult. The moderate coupling yields could originate from the coupling step between the +3 titanium catalyst and the aliphatic aldehyde. If $Cp_2TiCl$ (III) is solely responsible for reductively coupling with the aliphatic substrate, the stoichiometric reducing metal may be inconsequential to the $Cp_2TiCl_2$/M catalyzed reactions with aliphatic systems. The stoichiometric metal may play a significant role in the rate or selectivity of these reactions through the formation of a different trimetallic intermediate.

When designing optimization experiments for the aliphatic aldehydes, pre-catalysts other than $Cp_2TiCl_2$ were examined, and reducing metals in addition to manganese were utilized. Although manganese was successful in forming the $Cp_2TiCl$ (III) catalyst and may have created an ideal trimetallic intermediate for aromatic aldehydes, it may not be appropriate with different metallocenes and substrates. Hence, several metal reducing agents in addition to manganese were investigated. Control reactions with aliphatic substrates were run first to determine if the metals reduced the substrate in the absence of catalyst (Table 3-4). Metals that did not form pinacol product in the control reactions were used in combination with titanium, niobium, and zirconium metallocenes (*vide infra*). Because the aliphatic aldehydes are more difficult to reduce, the probability that these more active metals would directly reduce the aliphatic substrates was lower. Control reactions were performed with each of the metal reducing agents to determine if the metal was capable of reductively coupling the aldehyde in the absence of catalyst. Four metals, zinc, manganese, magnesium and aluminum, were examined.

**Table 3-4: Control reactions using cyclohexanecarboxaldehyde[a,b]**

| Metal | Product[c] |
|---|---|
| Zinc | - |
| Zinc[d] | - |
| Magnesium | - |
| Manganese | - |
| Aluminum[e] | + |
| Aluminum[e,f] | - |

[a] Conditions: cyclohexanecarboxaldehyde, metal, TMSCl, THF, ambient temperature; [b] G.C. used to monitor reactions, taken after 24 h; [c] - indicates no disilyl ether formed, + indicates disilyl ether formed; [d] activated; [e] amalgom; [f] 0°C.

Zinc was used in both an unactivated and activated (treated with HCl to remove any oxide coating) form for control reactions. In both control reactions, the zinc did not couple the aliphatic aldehyde. The aluminum used in the control reactions was activated using $Hg(NO_3)$.[19]

**Scheme 3-7: Activation of Aluminum metal**

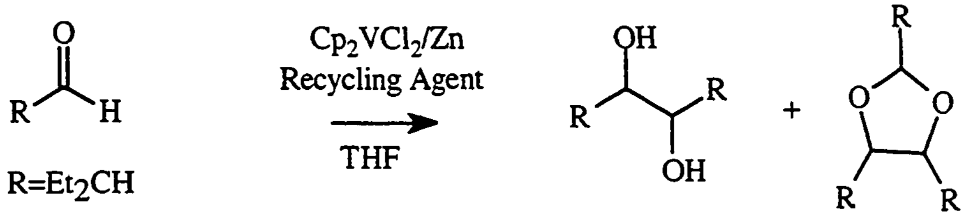
$$\text{Aluminum} \xrightarrow[H_2O]{Hg(NO_3)} Al(HgNO_3)$$

It was discovered that at ambient temperature the activated aluminum was capable of generating the pinacol product in the absence of catalyst. However, if the temperature was reduced to 0°C, no pinacol product was observed.

Manganese and magnesium, which were successful in reactions using benzaldehyde and $Cp_2TiCl_2$ (i.e. did not reduce PhCHO), were evaluated in control reactions as well to verify that they were not capable of generating pinacol product in the absence of catalyst. Through the control reactions, manganese, magnesium, and zinc (activated and unactivated) remained potential candidates for future pinacol reactions at ambient temperature with the aliphatic aldehydes. Activated aluminum was also a potential candidate in pinacolizations at 0°C. All four of these metals were employed in several pinacolizations with aliphatic aldehydes (*vide infra*).

*Recycling Agents:* A variety of recycling agents in addition to TMSCl have been reported for pinacol coupling reactions. The success that was achieved with these other reagents was critical in our decision to evaluate other recycling agents. For instance, Hirao indicated that $PhMe_2SiCl$ was capable of increasing diastereoselectivity in vanadium-catalyzed pinacol couplings.[14]

**Scheme 3-8: Vanadium-catalyzed reactions with different silyl recycling agents**

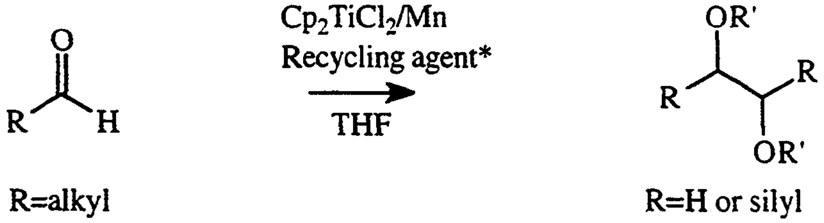


| Recycling Agent | *dl:meso*[a] |
|---|---|
| TMSCl | 88:12 |
| $PhMe_2SiCl$ | 96:4 |

a=diol

Gansauer also achieved better results with an alternative recycling agent. In his work with aromatic aldehydes, collidinium chloride was utilized and found to improve diastereoselectivites in some cases.[8,9] Both of these recycling agents were utilized in several of our pinacol reactions with aliphatic aldehydes (Scheme 3-9). TMSI was also examined as a recycling agent.

**Scheme 3-9: Coupling reactions with various recycling agents**



*Recycling agents: TMSCl, TMSI, $PhMe_2SiCl$, Collidine/HCl

The motivating factor for choosing this particular reagent lay in the electronic nature of the halide. The iodide will be a better leaving group than the chloride in TMSCl. The use of TMSI could increase the reaction rate for coupling aliphatic and aromatic aldehydes. Results with these recycling agents are described below.

TMSI was examined with both cyclohexanecarboxaldehyde and hexanal in pinacol coupling reactions. It was hypothesized that the iodide would be a better leaving group and would improve the rate of coupling provided that metathesis of titanium-pinacolate with the recycling agent was rate limiting. However, in both cases, the TMSI reacted with the solvent, THF, instead of the aliphatic substrate.

**Scheme 3-10: Side reaction of THF and TMSI**

Since THF was interfering with the reaction, an experiment was run using methylene chloride as solvent. In this reaction, no pinacol product was observed. Further studies with TMSI were therefore not pursued.

A bulkier silyl reagent, $PhMe_2SiCl$, was investigated in an effort to improve diastereoselectivity. Hirao found that a more hindered silyl reagent improved diastereoselectivity for the less hindered aliphatic aldehydes although the origin of this modest effect is unclear.[14] Both cyclohexanecarboxaldehyde and hexanal were evaluated with this recycling agent. In both instances, the reactions were slower and significant amounts of unreacted substrate were observed in the G.C. Furthermore, several side products were observed in the G.C. and no improvement in diastereoselectivity was noted for either aliphatic aldehyde.

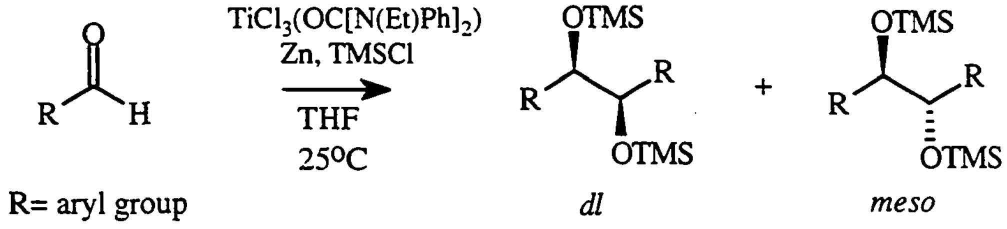
Finally, collidinium chloride was investigated with the substrate, isobutyraldehyde. In this reaction, a significant amount of unreacted aldehyde was observed in the G.C. after 48 hours. Moreover, a number of impurities were present along with the desired disilyl ether. Because the impurities were so numerous, a *dl:meso* ratio could not be determined for this reaction.

A number of recycling agents were studied in an attempt to improve both reaction rates and diastereoselectivities. Unfortunately, both of these recycling agents failed to produce the desired effect. The TMSI, as mentioned earlier, reacted more readily with THF than with the presumed trimetallic intermediate. As for the collidinium chloride, it was speculated that the increased steric bulk of this recycling agent may prevent it from approaching the pinacolate intermediate to regenerate $Cp_2TiCl_2$ and produce the pinacol product.

The $PhMe_2SiCl$ reagent, based on Hirao's results, could possibly improve diastereoselectivity with the less hindered aldehydes like hexanal. However, in reactions using it, no improved selectivity was observed. While Hirao indicated that this recycling agent improved diastereoselectivity,[14] the catalytic cycles proposed to date indicate that diastereoselectivity is set (when the C-C bond is formed between carbonyl substrates) before the recycling agent participates. Again, $PhMe_2SiCl$ did not improve either the reaction rate or the diastereoselectivity in our system. If the recycling step was rate determining, the increased steric bulk of the recycling agent may have prevented it from effectively reacting with the titanium-pinacolate intermediate. In the end, the optimal recycling agent remained TMSCl.

*Additives:* A few additives have been utilized in pinacol coupling reactions and provided literature precedents for us to investigate additives in our system. Gansauer included $MgBr_2$ in several of his catalytic pinacol couplings with aromatic aldehydes (Conditions: aromatic aldehyde, $Cp_2TiCl_2$, Zn, TMSCl, $MgBr_2$, THF).[2,7] Higher diastereoselectivity was achieved with this additive, and the results with $MgBr_2$ were interpreted in terms of a tighter trimetallic titanium catalyst that was formed by replacing zinc with magnesium. Nelson's group also utilized additives in his pinacol system to improve yields and selectivities.[3] They found that a combination of the $TiCl_3(THF)_3$ complex and a Lewis base, 1,3-diethyl-1,3-diphenylurea (DEPU) produced high yields (83-95%) and diastereoselectivities (67:33 to 91:9) with aromatic aldehydes.

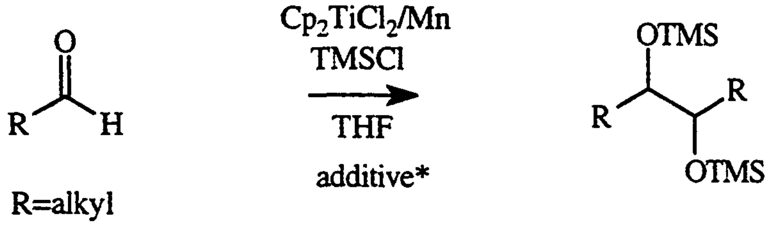
**Scheme 3-11: Titanium-DEPU complexes in coupling reactions**



From the results of Gansauer and Nelson, we decided to investigate amines and Lewis acids for their possible contribution to the reaction rate of aliphatic couplings and for their potential assistance in diastereoselectivity.

A variety of additives were included into the standard pinacol procedure used with cyclohexanecarboxaldehyde (Scheme 3-12). Both amines (Lewis bases) and Lewis acids were used as additives. It was hypothesized that an amine, by coordinating to the titanium atom as a Lewis base, could donate its electron density to the reduced titanium complex thus making the complex more electron rich. With the increase in electronic density, the complex (when reduced to its +3 state) would be a stronger reductant for the aliphatic substrates. However, in the reactions using both triethylamine and diisopropyl amine, the reaction rate was slower than the rate in which no amine was present.

**Scheme 3-12: Coupling reactions with additives**



*additives: $Et_3N$, $(iPr)_2NEt$, $MgBr_2$, $ZnCl_2$, $FeCl_3$, and $SnCl_4$

A possible explanation could be that coordination between the amines and the reduced titanium intermediate occurred, but the resulting trimetallic intermediate with coordinated amines may be too hindered to efficiently couple carbonyl species.

As for the Lewis acids, it was suggested that a different trimetallic intermediate might be generated by an inorganic additive. The trimetallic intermediate without an additive places manganese between the two titanium atoms (Ti-Mn-Ti). With a Lewis acid present, the manganese might be replaced by the metal from the Lewis acid to create a new trimetallic intermediate. A different metal bridging the two titanium atoms opens up the possibilities for improving diastereoselectivity. A metal smaller than manganese or one that forms tighter bonds with titanium would make the trimetallic intermediate smaller. Since the carbonyl substrates coordinate to the titanium, this smaller trimetallic intermediate might increase the steric hindrance between the aryl or alkyl groups of the carbonyl substrates favoring the *anti* geometry in the transition state and *dl* product. Furthermore, it was hypothesized that the Lewis acids would coordinate the carbonyl substrates making them more easily reduced by the active (III) metallocene catalyst.

**Table 3-5: Pinacolization using Additives[a]**

| Additive | Time[b] | Product:Aldehyde[c] |
|---|---|---|
| $MgBr_2$ | 48 h | 2:1 |
| $ZnCl_2$ | 72 h | 17:1 |
| $FeCl_3$ | 48 h | 1:11 |
| $SnCl_4$ | 48 h | 1:18 |
| $Et_3N$ | 72 h | 1:3 |
| $(iPr)_2NEt$ | 72 h | 3:1 |

[a] Conditions: cyclohexanecarboxaldehyde, manganese, TMSCl, $Cp_2TiCl_2$, THF, Lewis acid or base. [b] when reaction was halted. [c] ratio determined by G.C. after reaction was halted.

The Lewis acids tested include: $MgBr_2$, $ZnCl_2$, $FeCl_3$, and $SnCl_4$ and the Lewis bases include: $Et_3N$ and $(iPr)_2NEt$. In all cases however, no increase in reaction rate or diastereoselectivity was achieved; at most, a *dl:meso* ratio of 2:1 was achieved with the additives evaluated. With some of the Lewis acids tested, a substantial amount of product was formed after several days (Table 3-5). Reactions using Lewis acids $MgBr_2$ and $ZnCl_2$ and Lewis base $(iPr)_2NEt$ possessed more product than aldehyde based on G.C. analysis. In all of these instances, it should be noted that several side products were observed in the G.C. and may have contributed to the consumption of aldehyde. Both $FeCl_3$ and $SnCl_4$ generated only trace amounts of product according to G.C. Triethylamine produced slightly more product than the iron and tin additives; however, product formation was not substantial enough to warrant further investigation. The failure of the Lewis acids may be attributed to generation of new trimetallic intermediates that were not conducive to pinacol coupling. The use of additives in pinacol couplings was halted at this stage.

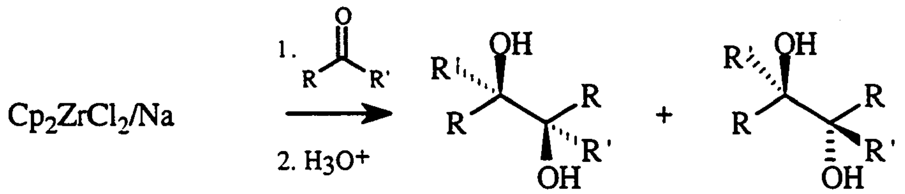
*Catalysts:* A variety of catalysts in addition to $Cp_2TiCl_2$ were studied in an effort to improve yields and diastereoselectivity with the aliphatic aldehydes. Catalysts were chosen because of their unique steric and electronic features which might impact yields and stereoselectivities. Another consideration in choosing particular catalysts was availability. Several catalysts, in addition to their unique chemical features, were commercially available. Others catalysts were provided by Dr. Ron Halterman and his group members. And finally, a few catalysts were synthesized in the Nicholas laboratory.

*Niobium and zirconium based catalysts:* Variations in the electronic character of the catalysts (compared to $Cp_2TiCl_2$) included alkyl substituted cyclopentadienyl rings and non-titanium-based metallocenes. Since aliphatic aldehydes are more difficult to reduce, it was hypothesized that a stronger reducing metallocene (in its active +3 state) could potentially increase the rate of pinacol coupling for aliphatic substrates. The oxidation potentials (one electron, +3 to +4) for $Cp_2TiCl_2$ and $Cp_2ZrCl_2$ in acetonitrile are 1.75 V and 1.84 V respectively.[20] Based on these potentials, reduction of $Cp_2ZrCl_2$ to its +3 state is more difficult than reduction of $Cp_2TiCl_2$. However, once reduced to $Cp_2ZrCl$ (III), this metallocene will likely be a stronger reducing agent than $Cp_2TiCl$ (III).

An oxidation potential is not available for $Cp_2NbCl_2$, but it has been shown that strong reducing agents are necessary to reduce $Cp_2NbCl_2$ to $Cp_2NbCl$. Sodium naphthalene is one of the best methods to generate the +3 niobocene compound.[21] Niobocene dichloride appears to be more difficult to reduce than titanocene dichloride based on the reducing agents employed with each metallocene. Once in the +3 state, however, niobocene should be more effective at reductively coupling to carbonyl substrates than the analogous titanocene (III) complex. Both $Cp_2ZrCl_2$ and $Cp_2NbCl_2$ were likely candidates for pinacolizations with aliphatic substrates.

Changing the catalyst to the zirconium and niobium complexes seemed like a straight forward solution; however, it should be noted that one complication still remained. While the +3 active states of the zirconium and niobium complexes were deemed more reactive, reducing them from their initial +4 state to the desired, active state would be more difficult. Literature precedents for $Cp_2ZrCl_2$ and variations of niobium-mediated pinacol couplings were critical in our decision to evaluate these two different metallocenes derivatives. Stoichiometric amounts of zirconocene dichloride and Na(Hg) have recently been reported to generate pinacol products with some stereoselectivity (Scheme 3-13).[22]

**Scheme 3-13: $Cp_2ZrCl_2$/Na(Hg) mediated couplings**

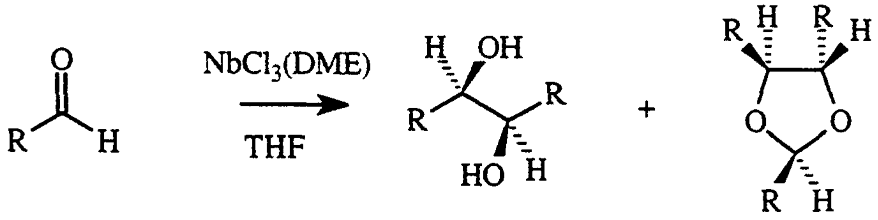


| **Substrate** | **Yield** | ***dl:meso*** |
|---|---|---|
| benzaldehyde | 80% | 65:35 |
| pentanal | 66% | 88:12 |
| acetophenone | 78% | 50:50 |

Substrates examined with this system included both aromatic and aliphatic aldehydes as well as aromatic ketones.

Evidence for pinacol couplings of aliphatic aldehydes with niobium complexes made $Cp_2NbCl_2$ a potential catalyst. The niobium (III) compound, $NbCl_3$(DME), couples aliphatic aldehydes to form a mixture of diol and acetal ($\text{yields}_{(\text{diol + acetal})}$ = 71 to 84%).[4,5]

**Scheme 3-14: NbCl3(DME) mediated couplings**

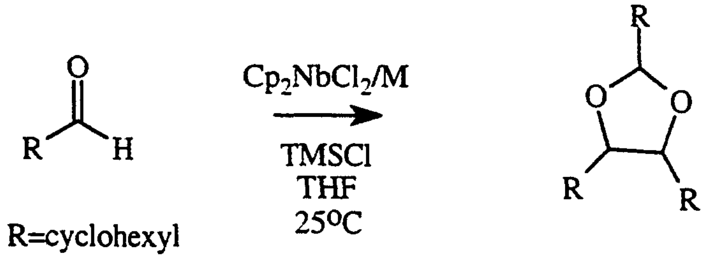


In the majority of instances, the acetal was the major product. The *dl:meso* ratios for the diol ranged from 88:12 to 95:5. The *dl:meso* ratio for the acetal product isolated ranged from 87:13 to 94:6.

From these literature examples, it was clear that both niobium and zirconium complexes were capable of inducing pinacol coupling with aliphatic substrates. While these results were positive, it should be noted that their systems used stoichiometric amounts of these metal complexes. Schwartz prepared the zirconium dimer using sodium metal before he combined it with the carbonyl moiety. To apply his system to our catalytic one would require that sodium metal and zirconocene dichloride be combined *in situ* with the carbonyl substrate and other reagents. More than likely, the sodium metal would competitively reduce the aliphatic aldehyde with the zirconocene dichloride catalyst. While this likely complication discouraged us from using Schwartz's exact reagents, it did not stop us from studying zirconocene dichloride in combination with different metal reducing agents (weaker than sodium). As for the system using $NbCl_3(DME)$, the niobium was already in the active +3 state necessary to perform the pinacol couplings. The $Cp_2NbCl_2$ used in our reactions was initially in the +4 state. Similar to the zirconocene complex, the $Cp_2NbCl_2$ complex needed suitable reducing metals to generate the desired +3 state.

Niobocene dichloride was evaluated with cyclohexanecarboxaldehyde in the Nicholas lab with several reactions.

**Scheme 3-15: Niobocene-catalyzed couplings**



In all instances, the acetal was formed instead of the disilyl ether. Diastereoselectivity for the acetal was highest when manganese was employed with niobocene dichloride. Moderate *dl:meso* ratios were achieved when magnesium and zinc were employed. $^{1}$H NMR for the *dl* isomer included two doublets of doublets at 3.18, and 3.34 and a doublet at 4.08 ppm. These resonances represented the ring protons. The ring protons for the *meso* acetals (two isomers) had absorptions at 3.58 and 4.41 ( both doublets) for one isomer and 3.64 and 4.61 (both doublets) for the other isomer. MS further verified the formation of acetal. Mass to charge ratios at 319 ($M^{+}$-1,1.6) and 237 ($M^{+}$-83,85.2) confirmed the presence of acetal.

Several metals were utilized to reduce the niobocene dichloride to its active +3 state.

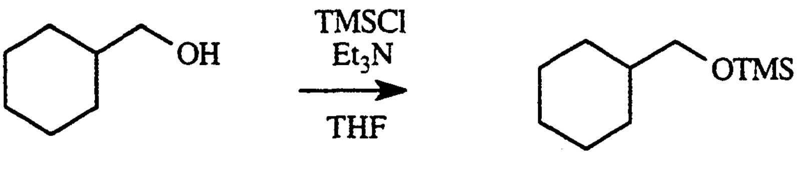
**Table 3-6: Cp$_2$NbCl$_2$ coupling reactions[a,b]**

| **metal** | **aldehyde:product[d]** | ***dl:meso*[c]** |
|---|---|---|
| manganese | 7:1 | 100:0 |
| magnesium | 7:1 | 3:1 |
| zinc | 6:1 | 2:1 |

[a] conditions: cyclohexanecarboxaldehyde, TMSCl, THF, ambient temperature; [b] G.C.'s taken after 24 h to monitor progress; [c] acetal product. [d] Ratio of aldehyde to product after 24 h when reaction was halted.

The initial study with niobocene dichloride indicated that a significant amount of unreacted aldehyde was still present after 24 hours as well as a significant amount of a side product judging by GC and NMR.

**Scheme 3-16: Silylation of cyclohexylmethanol**

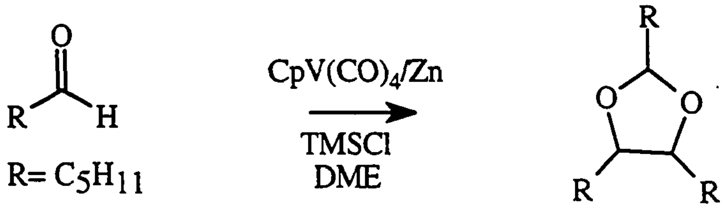


**8**

It was speculated that a competitive, direct reduction of the aldehyde to the alcohol and subsequent silylation was occurring. An authentic sample of the mono-silyl ether was prepared from cyclohexylmethanol (Scheme 3-16).[23] With this compound in hand, comparisons were made between it and the samples isolated from the $Cp_2NbCl_2$ catalyzed reactions. Identical peaks in the GC and NMR verified that some of the aldehyde was being reduced directly to the alcohol and then silylated.

The initial experiments clearly indicated that niobocene dichloride had the potential to improve diastereoselectivities of the acetal; however, yields needed to be optimized. Additional experiments were performed in an effort to accomplish this.

**Scheme 3-17: Variations in TMSCl concentration**



| TMSCl | Yield |
|---|---|
| 0.5 equivalents | 48% |
| 1.0 equivalents | 84% |

Hirao indicated (Scheme 3-17) that the amount of TMSCl present in the vanadium catalyzed pinacol couplings influenced the amount of product generated.[13] In the absence of TMSCl, no coupling was observed; this result indicated that TMSCl was essential in the catalytic cycle. When the amount of TMSCl was doubled, the yield increased proportionally. Hirao suggested that TMSCl was likely to contribute during the reductive coupling reaction of the carbonyl substrates.

Reactions using varying amounts of TMSCl were run for our niobocene catalyzed system (refer to Table 3-7).

**Table 3-7: $Cp_2NbCl_2$/Mn reactions of various TMSCl concentrations[a,b]**

| TMSCl | Time | Aldehyde:Product[c] |
|---|---|---|
| 0 | 24h | 1:0 |
| 1.1 mmol | 24h | 7:1 |
| 2.2 mmol | 24h | 7:1 |

[a] conditions: cyclohexanecarboxaldehyde, $Cp_2NbCl_2$, Mn, THF, ambient temperature; [b] G.C.'s used to determined aldehyde:product ratio; [c]aldehyde not completely consumed based on ratios when reaction was halted.

Altering the concentration of TMSCl did not improve the yields for the reactions with $Cp_2NbCl_2$. A few other improvement attempts were made. The amount of solvent used was reduced in one reaction, and in another, the reaction mixture was refluxed. In both of these instances, the yields did not improve and additional side products were observed by GC analysis. It is speculated that the low conversion of aldehyde in the niobium catalyzed pinacol reaction may have been the result of insufficient conversion of the $Cp_2NbCl_2$ to the active +3 state. As mentioned earlier, sodium naphthalene was the best method for reducing niobocene dichloride.[21] Therefore, the manganese, zinc, and magnesium evaluated as stoichiometric reducing agents may not have been effective in reducing the niobium complex. Another explanation for the low conversion of aldehyde to product is that the catalyst may have decomposed after several hours. This possibility is supported by the product:aldehyde ratios evaluated by G.C. over several days. The rate of conversion was fast for the first several hours of the reactions and gradually decreased after one to two days had passed. A simple observation was made for reactions that formed acetal instead of disilyl ether. It was noted that acetal formation occurred in the majority of the slower reactions. The formation of acetal in pinacol couplings will be expounded upon in chapter 5.

Zirconocene dichloride was also evaluated for pinacolization of cyclohexanecarboxaldehyde. This complex was used with magnesium, manganese, and activated aluminum reductants (refer to Table 3-8).

**Table 3-8: Zirconocene dichloride-catalyzed pinacol couplings[a,b]**

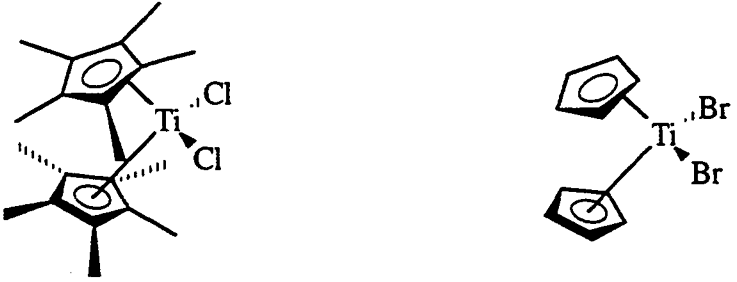
| **Metal** | **Aldehyde** | **Product** |
|---|---|---|
| Magnesium | 1 | 0 |
| Manganese | 1 | 0 |
| Aluminum[c] | 1 | 0 |

[a] Conditions: cyclohexanecarboxaldehyde, TMSCl, THF, ambient temperature; [b] G.C.'s taken after 48 h. [c] activated ($HgNO_3$) aluminum, reaction run at 0°C.

In all three instances, no pinacol product was produced according to G.C. analysis. This failure was attributed to the inability of the metals to effectively reduce zirconocene dichloride to its active +3 state. When the metals were combined with zirconocene dichloride and stirred for 20 to 30 minutes, there was no color change indicating a change of oxidation states. A color change was observed with $Cp_2TiCl_2$ and manganese in THF from red to green as $Cp_2TiCl_2$ was reduced to the +3 state. Hence, the $Cp_2ZrCl_2$/Mn, Mg, or Al(Hg) systems were thought to have produced little to no active catalyst.

*Achiral titanium-based complexes:* Several titanium-based complexes were examined in the Nicholas laboratory for their effectiveness in coupling aliphatic aldehydes. Both steric and electronic features of these complexes had the potential to increase diastereoselectivity and improve the reaction rate. Both permethylated titanocene dichloride **9** and titanocene dibromide **10** were studied (Table 3-9) for their potential electronic influence in pinacol reactions.

**Figure 3-3: Titanocene-complexes with special electronic features**



**9** **10**

The alkyl groups on the permethylated complex increase the electronic character of the titanium complex relative to titanocene dichloride.[24] Ideally, the more electron rich complexes, when reduced to the +3 state, should be more effective at reductively coupling with aliphatic substrates. In addition to being more electron rich, the permethylated catalyst is also sterically hindered and was evaluated in that respect as well.

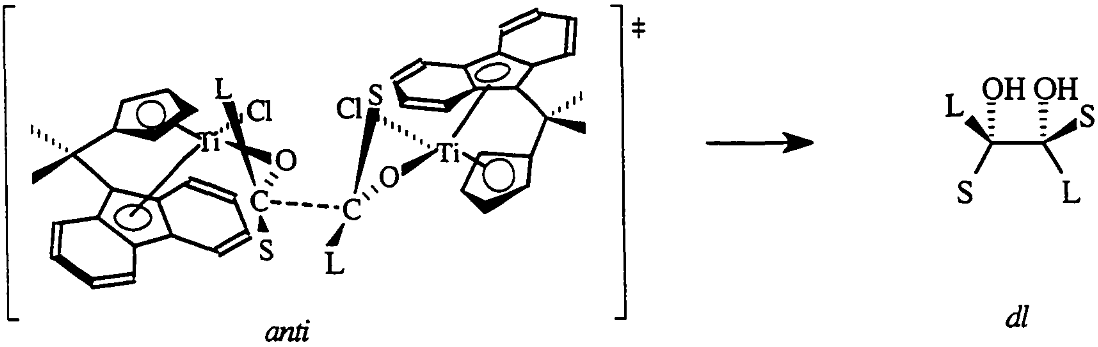
The titanium bromide complex was evaluated because of its electronic properties. The oxidation potentials (one electron, +3 to +4) for $Cp_2TiBr_2$ and $Cp_2TiCl_2$ are 1.70 V and 1.75 V respectively.[20] Thus, the reduction of $Cp_2TiBr_2$ (-1.70 V) from +4 to +3 should occur more readily than for $Cp_2TiCl_2$ (-1.75 V). However, once in the +3 state, the chloride compound should more readily undergo reductive coupling with the carbonyl substrate. The ability of the leaving group is another important factor. Bromide is a better leaving group than chloride. Therefore, formation of $Cp_2TiBr$ should occur more readily than formation of the chloride (III) intermediate. Both electrochemical data and leaving group ability indicate that formation of the +3 titanocene bromide complex is easier than formation of the chloride one. However, once in the +3 state, the chloride complex should be more likely to reductively couple.

Catalysts with unique steric features were also of interest in our optimization reactions with aliphatic substrates. As described earlier, the pinacol reaction probably goes through a bi- or trimetallic intermediate in which the stereochemistry is established. With the flexible nature of the aliphatic aldehydes, it was less likely for the alkyl groups on the aldehydes to position themselves *anti* to one another to eventually yield the *dl* isomer. Through the use of sterically hindered titanium catalysts, the bi- or trimetallic intermediate may force the alkyl groups from the aldehydes into the *anti* position with one another. The following suggested transition states with a representative hindered catalyst illustrate this idea:

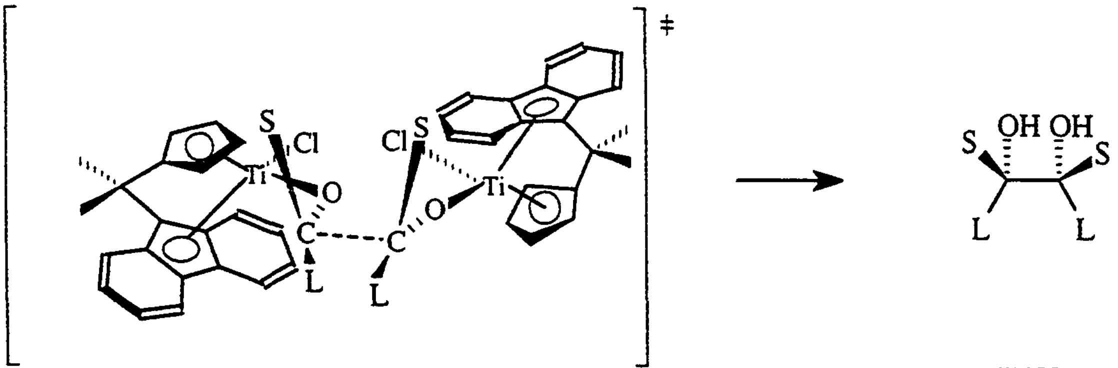
**Figure 3-4: Suggested Isopropylidene (flourenylcyclopentadienyl) titanium chloride transition states**

L = large group
S = small group

i. *anti* transition state:



ii. *syn* transition state:

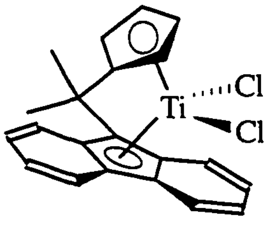


*syn* *meso*

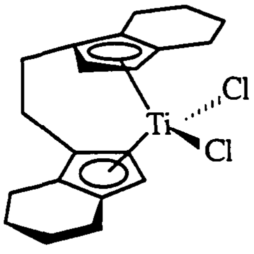
The varying ring sizes of the complex influence how two molecules of the catalyst combine to form the bi- or trimetallic intermediate. Ideally, the two molecules of catalyst will arrange themselves in the transition state so that the large fluorenyl groups on each molecule are *anti* to one another to minimize steric hindrance. With this lowest energy transition state, the large groups on the carbonyl substrate will be directed to the more open regions. This arrangement will place the large groups *anti* to one another to minimize steric hindrance leading to the *dl* isomer.

Titanium complexes that were conformationally constrained by a tether were studied as well. Dr. Ron Halterman synthesized complex 11[25-28] and Brintzinger's catalyst 12 was prepared by reduction of *rac*-ethylene-*bis*(indenyl)titanium dichloride.[29]

**Figure 3-5: Tethered titanium complexes**



**11**

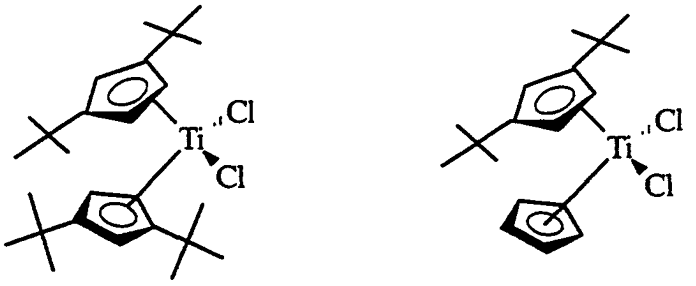


**12**

Generating a more sterically hindered and rigid catalyst could potentially improve diastereoselectivity. With these complexes, it is likely that one conformation dominates. The major conformation of the complex could lead to a specific bi- or trimetallic intermediate that would favor formation of the *dl* isomer (results in Table 3-9).

Two other titanium complexes possessing bulky groups were utilized for pinacol couplings as well. Both of these catalysts were synthesized in our laboratory.

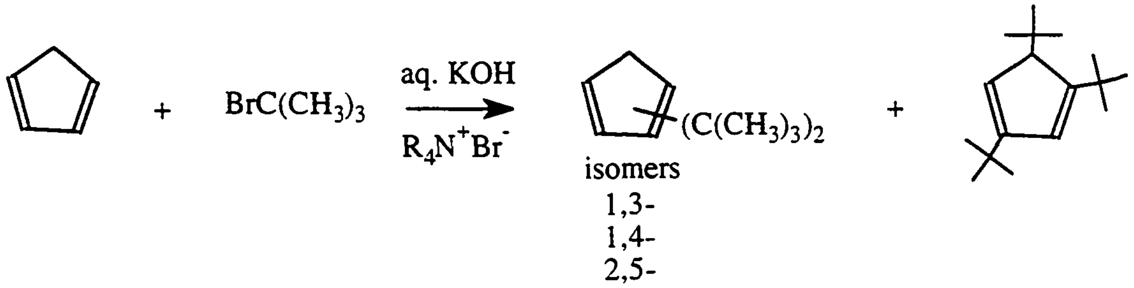
**Figure 3-6: di-*tert*-butyl substituted titanium complexes**



**13** **14**

The ligand, di-*tert*-butylcyclopentadiene, was synthesized using a phase transfer-catalyzed alkylation.[30] *Tert*-butyl bromide and cyclopentadiene were reacted with aqueous KOH and Adogen 464 (phase transfer catalyst, $R_4N^+Br^-$).

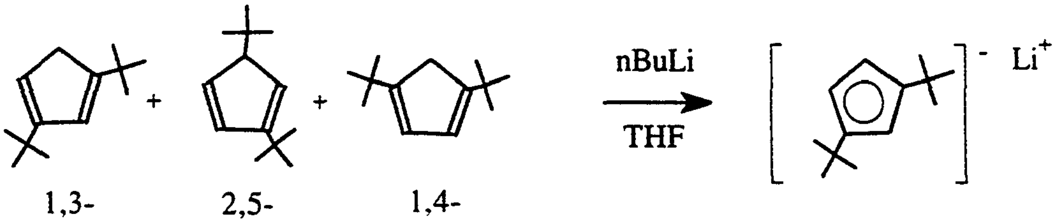
**Scheme 3-18: Preparation of di-*tert*-butylcyclopentadiene isomers**



Although Venier indicated that a tri-substituted isomer was also formed, only the di-substituted isomers were detected in our preparation of the ligand. Three isomers of the di-

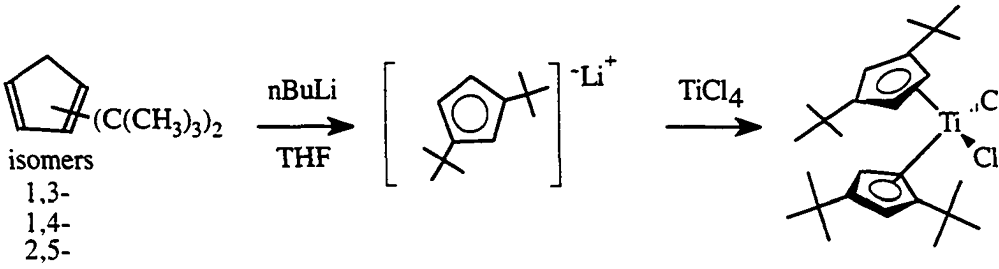
*tert*-butyl cyclopentadiene ligand were generated according to $^1$H NMR, GC and GC/MS; no purification was necessary since the next synthetic step involved deprotonation of the ligand. Upon deprotonation all three isomers were converted to a single anion.

**Scheme 3-19: Deprotonation of di-*tert*-butylcyclopentadiene isomers**



To synthesize the bis($\eta^5$-di-*tert*-butylcyclopentadienyl) titanium dichloride 13, the ligand was first deprotonated and then reacted with $TiCl_4$.[31]

**Scheme 3-20: Preparation of *bis*($\eta^5$-di-*tert*-butylcyclopentadienyl)titanium dichloride**



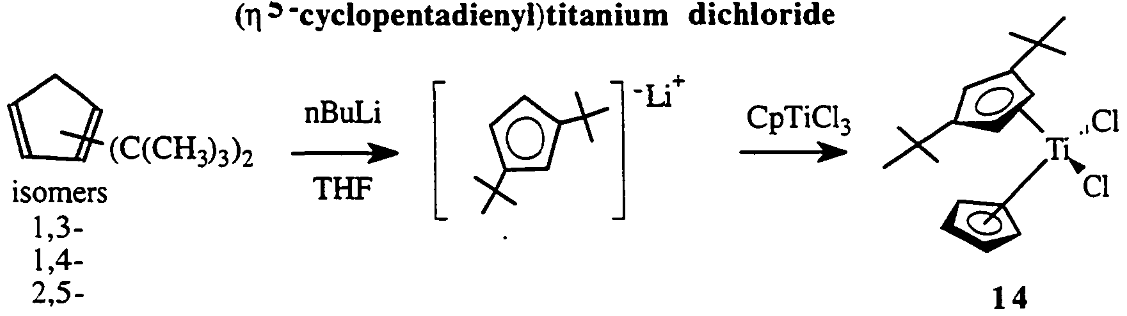
**13**

While some of the other catalysts evaluated have been expected to form bi- or trimetallic intermediates when in their +3 state, reports indicate that complex 13 remains a monomer when reduced to its +3 state.[31] The steric hindrance associated with 13 is believed to prevent the complex from forming a dimer.

Synthesis of the mixed ligand complex 14 followed a similar procedure. Complex 14 is unique in that its ligands are not identical. Moreover, one ligand is sterically hindered with two t-butyl groups, while the other is unsubstituted and thus unhindered. Like complex 11, it is hypothesized that in a bi- or trimetallic intermediate of complex 14, the 1,3-di-t-butylcyclopentadienyl ligands would be *anti* to one another. The hypothesized trimetallic intermediate should favor formation of the *dl* product.

It should be emphasized that 14 was a new compound and the procedure used to synthesize it was developed in the Nicholas laboratory. Deprotonation of the ligand was performed and followed by reaction with $CpTiCl_3$. The solution was heated to reflux solvent overnight and was concentrated the next day. Trituration of the remaining residue with a mixture of methylene chloride and benzene followed by flash chromatography produced 14 as a red solid. Both proton and carbon NMR verified that complex 14 had formed. The resonances for all the protons in 14 were singlets and were observed at 1.25 ppm (18 H), 6.54 ppm (2 H), 6.58 ppm (5 H), and 6.90 ppm (1 H). The carbon NMR spectrum revealed the expected number and absorption positions of all of the carbons in 14. Moreover, a high resolution FAB mass spectrum revealed a molecular ion for complex 14.

**Scheme 3-21: Preparation of ($\eta^5$-di-t-butylcyclopentadienyl) ($\eta^5$-cyclopentadienyl)titanium dichloride**

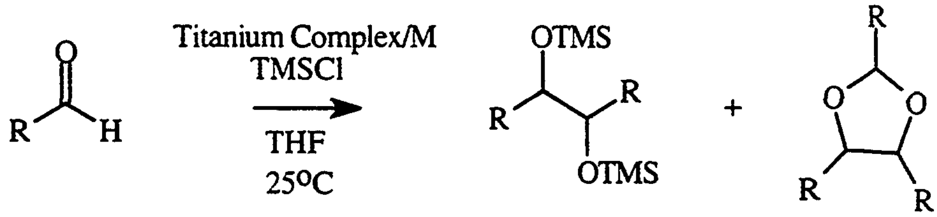


**14**

The required $CpTiCl_3$ was synthesized in some instances and was bought in other cases due to time constraints. The preparation of $CpTiCl_3$ involved reacting $TiCl_4$ with $Cp_2TiCl_2$ at an elevated temperature.[32] Once complexes 13 and 14 were prepared, they were evaluated in pinacol couplings of cyclohexanecarboxaldehyde.

The achiral titanium-based complexes (**9-14**) were combined with manganese in flasks under nitrogen. Distilled THF was added to each reaction vessel, and the solution was stirred for approximately 15 minutes.

**Scheme 3-22: Pinacolization with achiral titanocene derivatives**

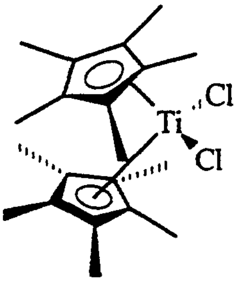


R=cyclohexyl
M = Mn or Zn
Titanium Complex = **9-14**

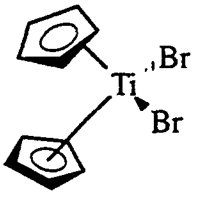
Next, TMSCl and cyclohexanecarboxaldehyde were added rapidly by syringe. The solutions stirred at ambient temperature and were monitored by G.C. The reactions ran from 48 hours to 4 days. When it appeared as though aldehyde was no longer being consumed, the reactions were stopped and worked-up with Celite filtrations followed by concentration and trituration with a mixture of petroleum ether and ether. NMR and GC/MS data revealed that disilyl ether and/or acetal had been formed. The results obtained with complexes **9-14** are summarized in Table 3-9. In all cases, the achiral titanium-based catalysts failed to produce yields as high as those achieved with $Cp_2TiCl_2$. Moreover, the reaction times were longer than with the original titanium catalyst in the standard procedure. Stereoselectivities were poor to good.

The titanium complexes evaluated possessed greater electronic density in some cases and/ or more hindered ligands. For the complexes with increased electronic density, reduction to the +3 state is expected to be more difficult.

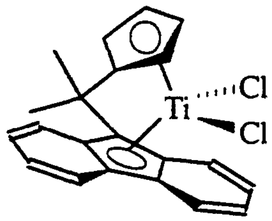
**Table 3-9: Pinacol couplings using derivatives of titanocene dichloride**[a,b]



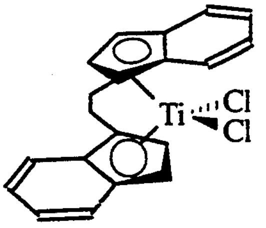
**9**



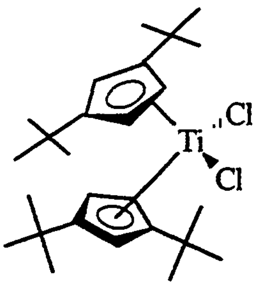
**10**



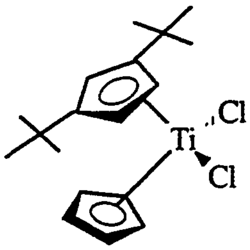
**11**



**12**



**13**



**14**

| **Catalyst** | **Product:Aldehyde** | ***dl:meso*** | |
|---|---|---|---|
| | | **disilyl ether** | **acetal** |
| **9** | 1:3 | 1:1 | na |
| **10** | 1:4 | na | 6:1 |
| **11**[c] | 1:8 | 2:1 | 2.5:1 |
| **12** | 1:4 | 5:1 | na |
| **13** | 1:5 | na | 6:1 |
| **14**[d] | 1:20 | na | yes[e] |

[a] conditions: cyclohexanecarboxaldehyde, Mn, TMSCl, THF, ambient temperature; [b] reactions monitored by G.C. for 48 h after which time product:aldehyde ratios indicate that aldehyde had not completely been consumed; [c] activated zinc instead of manganese; [d] run for 4 days. [e] ratio not determined

In these reactions, a distinct color change from red to green (as seen when $Cp_2TiCl_2$/Mn was used) was not observed. Manganese may have not been strong enough to reduce the titanium complexes to the +3 states.

Based on the observations and results using different metallocenes, it was discovered that the slower reactions produced acetal instead of disilyl ether. A further investigation comparing acetal and disilyl ether forming reactions was performed and is discussed in chapter 5. Based on the results found during mechanistic studies, a potential mechanism explaining acetal formation was developed and is discussed in chapter 5. While the acetal diastereoselectivity was encouraging, the low yields obtained and slow reaction times made the achiral titanocene derivatives poor pinacolization catalysts.

## Conclusions

The pinacolization of aliphatic aldehydes was investigated using the standard procedure developed with benzaldehyde ($Cp_2TiCl_2$/Mn/TMSCl/THF). A wide variety of aliphatic substrates were tested including α- 1°, 2°, and 3° aldehydes. Moreover, aldehydes possessing some unsaturation were included in this study. The yields were good and the diastereoselectivities were moderate. Little to no work had been reported for the stereoselective, catalytic pinacol coupling of aliphatic aldehydes. Hence, the results obtained in the Nicholas laboratory for aliphatic aldehydes were significant in that they represented the first catalytic system that successfully coupled aliphatic aldehydes to pinacol derivatives with some degree of diastereoselectivity.

It was hypothesized that the electronic and steric nature of the aliphatic aldehydes was responsible for the reduced diastereoselectivity and pinacol yields. The aliphatic substrates are more difficult to reduce relative to the aromatic aldehydes; thus, the rate of pinacolization was considerably reduced. Furthermore, some of the aliphatic aldehydes were less rigid and less hindered relative to benzaldehyde. When in the bi- or trimetallic transition state, these less hindered aliphatic aldehydes, like n-hexanal, showed lesser preference for positioning the alkyl groups *anti* to one another leading to the *dl* isomer.

Additional work was performed with the aliphatic aldehydes focusing on optimizing reactions by changing variables in the standard procedure. The variables examined included metal reducing agents, recycling agents, additives, and catalysts. The rates and selectivities obtained when testing each of these variables were not as good as the results obtained when the original model procedure was applied to aliphatic substrates.

Pinacolization was much slower when achiral titanium-based, zirconium and niobium metallocene complexes were employed. It was thought that the increased electronic density of each complex, relative to $Cp_2TiCl_2$, may have been a contributing factor to the decrease in pinacolization efficiency. The stoichiometric reducing metal, manganese, may not have been effective in reducing the complexes from their +4 states to the desired +3 states. Because of this problem encountered, additional metal reducing agents were evaluated in control reactions and in combination with these catalysts. Unfortunately, the metals investigated either performed the pinacol coupling without the catalyst present or were not effective at reducing the catalyst to the +3 state.

Additional recycling agents as well as Lewis acid and base additives were incorporated into the pinacol reactions with aliphatic aldehydes. With the recycling agents, it was postulated that more reactive silyl agents or even the collidinium chloride reagent would increase the rate of the reaction. This result was not observed; in fact, the rate of reaction decreased with the additional recycling agents tested. One possible explanation for the collidinium chloride as well as the $PhMe_2SiCl$ results is that the sterically hindered nature of these two reagents (relative to TMSCl) prevented them from effectively approaching the bi- or trimetallic intermediate to release the disilyl ether product and reform the catalyst in its +4 state. As for the TMSI, it was not sterically hindered but reacted with the solvent medium and was therefore ineffective at recycling the catalyst.

The purpose of the additives was to increase the rate of the reaction or selectivity. With the amine Lewis bases, it was speculated that it would coordinate to the reduced form of titanocene thus altering the expected bi- or trimetallic intermediate. It is possible that in coordinating to the active titanium intermediate, the amines may have made the intermediate to sterically crowded for the carbonyl groups to approach and undergo coupling. Lewis acids were also unsuccessful in improving pinacolization. Ideally, the Lewis acids would coordinate to the carbonyl substrate thus increasing the likelihood that it would be reductively coupled with the titanocene dichloride. Furthermore, it was hoped that the addition of an additive could improve diastereoselectivity as was observed with some of Gansauer's work.[1] One hypothesis can be used to explain the failure of the inorganic additives. The Lewis acids may have formed trimetallic intermediates that were not as conducive for pinacol coupling as the original Ti-Mn-Ti intermediate.

Titanium complexes as well as niobium and zirconium complexes were investigated with the aliphatic substrates. Both titanium complexes and $Cp_2NbCl_2$ showed improved selectivities for the pinacol acetal. Again, $Cp_2ZrCl_2$ induced no pinacolization at all because the stoichiometric metal reducing agents employed, whether manganese, magnesium, activated zinc, or aluminum, were not effective in reducing zirconocene to its +3 state. Our initial observation for the formation of acetal was that it tended to be generated in reactions that were slow. Mechanistic studies were performed to determine that pathway through which acetal was formed, and a detailed explanation of these studies will be presented in chapter 5.

While the original $Cp_2TiCl_2$-based system still was more effective, a few worthwhile results came during these studies. For instance, upon examining different catalysts with the optimal procedure, it was discovered that the pinacol-derived acetal was being formed with a high degree of diastereoselectivity. This result was interesting and led to additional studies probing the mechanism (chapter 5) that generated acetal instead of disilyl ether.

## Future Directions

Numerous variables were examined in an effort to improve both yields and selectivities for pinacolization of aliphatic aldehydes. Moderate improvements were made in the reactions. Future work in optimization experiments can be envisioned. For instance, finding suitable conditions that would allow both zirconocene and niobocene dichloride to induce coupling with aliphatic aldehydes is of interest. Both of these metallocenes are more difficult to reduce to the +3 state than titanocene dichloride. However, once in the +3 state, the metallocenes offer greater reducing ability than titanocene (III) chloride. Stronger reducing agents should be explored to determine if the niobium and zirconium metallocenes can be effectively reduced to the +3 state without directly reducing the carbonyl substrate.

Another area of interest that may be explored in the future is the pinacolization of aromatic ketones. A combination of zirconocene dichloride and activated aluminum was briefly tested with acetophenone during the pinacol project and was found to produce a trace amount of pinacol product along with several side products (based on G.C.). Additional work with ketones may be explored in the future using other catalyst and reducing systems.

## Experimental

### *General Methods*

The majority of starting materials were commercially available. Isopropylidene(fluorenylcyclopentadienyl) titanium dichloride[25-28] was synthesized by Dr. Ron Halterman. *Bis*(η5-di-t-butylcyclopentadienyl) titanium dichloride[30,31] was synthesized using a literature procedure. Collidinium chloride,[33] trimethylsilyl cyclohexylmethyl ether,[23] ($\eta^5$-cyclopentadienyl) titanium trichloride,[32] Brintzinger's catalyst,[29] Al(Hg),[19] and authentic samples of both *dl* and *meso* *bis*(cyclohexyl)-1,2-ethanediol[16] were also synthesized using literature methods. Tetrahydrofuran, diethyl ether, and DME were distilled under nitrogen from sodium and benzophenone; and, methylene chloride and benzene were distilled under nitrogen from $CaH_2$. Amines were distilled under nitrogen from potassium hydroxide and at atmospheric pressure. Glassware was oven dried (125°C) and flushed with nitrogen before use. Liquids were transferred using syringes, and all solids were manipulated within the dry box.

$^1$H NMR and $^{13}$C NMR were obtained using a Varian XL-300 or a Varian Unity Inova-400 instrument. All NMR samples were dissolved in $CDCl_3$ or $d_6$-benzene. A Hewlett Packard 5790A gas chromatograph using a 3m column packed with OV-101 was used for monitoring reactions. GC//MS were obtained on a Hewlett Packard 5985 GC/MS instrument.

Both gravity and flash chromatography techniques were employed. For gravity silica columns, the silica gel was 60 Å or 70-230 mesh. Flash chromatography utilized silica gel with particle sizes from 32-63. Petroleum ether, used in combination with diethyl ether for chromatography, was distilled to remove any high boiling impurities.

## Standard Procedure for Pinacol Coupling of Aliphatic Aldehydes

Titanocene dichloride (0.20 mmol, 50 mg) and manganese (50 mesh, 1.2 mmol, 66 mg) were added to a side arm round bottom flask under nitrogen. Distilled THF (20 ml) was added and the mixture was stirred for 15 min while changing from red to green. Chlorotrimethylsilane (2.2 mmol, 0.28 ml) was added *via* syringe followed by the aldehyde (2.0 mmol, 0.20 ml) and the mixture was stirred at 25 °C from 15 to 48 h depending on the aliphatic substrate. Aliquots (approx. 0.5 ml) were removed while the reaction was in progress. The aliquots were filtered through Celite, concentrated under a stream of nitrogen, triturated with 4:1 petroleum ether:ether, and filtered through Celite again. Next, the aliquots were injected onto the G.C. to monitor the reaction progress. Once the GC analysis indicated that all the aldehyde had been consumed, the mixture was worked-up. The volatiles were removed by rotary evaporation, the residue was triturated with 4:1 petroleum ether/ether, and the washings filtered through Celite. Concentration of the filtrate produced the crude products as orange or yellow oils. Further purification was accomplished by flash chromatography over silica gel using petroleum ether/ether as eluant providing the pinacol-*bis*-silyl ethers as colorless oils. The products were characterized by $^1$H and $^{13}$C NMR and mass spectrometry.

*6,7-bis(trimethylsiloxy)-dodeca-4,8-diene (1)*

GC & NMR purity ≥ 99%; yield: 45%; *dl:meso* : 2:1; *$^1$H NMR* ($CDCl_3$) δ maj + min: 0.83-0.89 (m, 12H), 1.33-1.38 (m,8H), 1.96 (m, 8H), 5.47-5.58 (m, 4H); min: 0.05 (s, 18H), 3.84 (d, J=6 Hz, 2H), 5.35 (dd, J=4.8 Hz, 1.2 Hz, 2H); maj: 0.08 (s, 18H), 3.87 (d, J=6 Hz, 2H), 5.39 (dd, J=4.8 Hz, 1.2 Hz, 2H); *$^{13}$C NMR* ($CDCl_3$) δ maj + min: 0.36, 0.95, 10.69, 13.58, 22.26, 29.64, 34.30, 129.94, 130.58, 131.99; ($d_6$-benzene) δ additional peak at 78.0; *GCMS* m/e (relative intensity) isomers not resolved by GC: 171.1 ($M^+$-171.1, 100)

*6,7-bis(trimethylsiloxy)-dodecane (2)*

GC & NMR purity ≥ 92%; yield: 80%; *dl:meso* : 1.5:1; *$^1$H NMR* ($CDCl_3$) δ maj + min: 0.09 (s, 36H), 0.87 (t, J=6.8 Hz, 12 H), 1.18-1.32 (m, 16H), 1.38-1.39 (m, 8H), 1.50 - 1.55 (m, 8H); maj: 3.47-3.50 (m, 2H) ; min: 3.51-3.52 (m, 2H) ($d_6$-benzene) δ min: 3.63 (d, J=5.2 Hz, 2H); maj: 3.73 (d, J=8.4 Hz, 2H); *$^{13}$C NMR* ($CDCl_3$) δ maj + min: 0.48, 1.27, 14.09, 22.59, 25.54, 25.99, 30.46, 31.82, 32.97, 32.69, 34.02, 73.00, 75.33 *GCMS* (12 ev EI) m/e (intensity): GC peak 1: 331.3 ($M^+$-15, 0.6), 173.1 ($M^+$-173.1, 100); GC peak 2: 331.3 ($M^+$-15.1, 1.2), 275.2 ($M^+$-0.56, 0.8), 173 ($M^+$-173.1, 100)

*2,3-bis(trimethylsiloxy)-1,4-diphenylbutane (3)*

GC & NMR purity ≥ 80%; yield: 93%; *dl:meso* : 3:1; $^{1}$*H NMR* (CDCl$_3$) δ: maj + min: 3.73-3.75 (m, 4H), 7.15-7.40 (m, 20H); min: -0.24 (s,18H), 2.65 (dd,J=9.2 Hz. 13.2 Hz. 2H), 2.89 (dd, 3.6 Hz, 13.4 Hz, 2H); maj: -0.20 (s,18H), 2.54 (dd, J=9.2 Hz, 9.6 Hz, 2H), 3.05 (broad d, J=12 Hz, 2H); $^{13}$*C NMR* (CDCl$_3$) δ min + maj: 0.29, 0.76, 38.43, 40.91, 74.01, 75.51, 127.36, 128.83, 129.80, 138.19; *GCMS* (12 ev EI) m/e (intensity): isomers not resolved by GC: 295 ($M^+$-91.2, 61.2), 206.1 ($M^+$-180.1, 6.6), 193.1 ($M^+$-193.1, 100)

*1,2-bis(trimethylsiloxy)-1,2-dicyclohexylethane (4)*

GC & NMR purity ≥ 98%; yield: 81%; *dl:meso* : 2:1; $^{1}$*H NMR* (CDCl$_3$) δ maj + min: 0.8-2.0 (m, 44H), 3.30 (d, J=6 Hz, 4H); maj: 0.10 (s, 18H); min: 0.11 (s, 18H); (d-$_6$benzene) δ maj: 3.34 (d, J=4 Hz, 2 H); min: 3.49 (d, J=8 Hz, 2H); $^{13}$*C NMR* (CDCl$_3$) δ maj + min: 0.90, 1.09, 26.15, 26.30, 26.63, 29.92, 30.62, 31.88, 39.10, 39.77, 78.30, 78.80; *GCMS* (12 ev EI) m/e (relative intensity): GC peak 1 185.1 ($M^+$-185.1, 100): GC peak 2: 185.1 ($M^+$-185.1, 100)

*3,4-bis(trimethylsiloxy)-2,5-dimethylhexane (5)*

GC & NMR purity ≥ 98%; yield: 60%; *dl:meso* : 2.5:1; $^{1}$*H NMR* (CDCl$_3$) δ maj: 0.10 (s, 18H), 0.08 (d, J=6.4 Hz, 6H), 0.84 (d, J=6.4 Hz, 6H), 1.80 (m, 2H), 3.26 (d, J=5.6 Hz, 2H); min: 0.10 (s, 18H), 0.88 (d, J=7.6 Hz, 6H), 0.89 (d, J=7.8 Hz, 6H), 1.88 (m, 2H), 3.38 (s, 2H); $^{13}$*C NMR* (CDCl$_3$) δ maj + min: 0.79, 1.03, 16.11, 19.51, 20.45, 21.11, 29.94, 30.14, 79.00, 79.85; *GCMS* (12 ev EI) m/e (intensity): GC peak 1: 247.3

($M^+$-43, 1.5), 145.1 ($M^+$-145.1, 100); GC peak 2: 275.2 ($M^+$-15, 1.1), 247 ($M^+$-43, 19.7), 158 ($M^+$-132.2, 1.6), 146.2 ($M^+$-144, 100)

*3,4-bis(trimethylsiloxy)-2,5-diphenylhexane (6)*

GC & NMR purity ≥ 95%; yield: 47%; *dl:meso* : 2:1:1:1; *$^1H$ NMR* ($CDCl_3$) δ maj: -0.130 (s, 18H), 1.10-1.15 (m, 6H), 2.82-2.96 (m, 2H), 3.65 (d, J= 5.0 Hz, 2H), 7.00-7.40 (m, 10 H); min 1: -0.22 (s, 18H), 1.15 (d, J= 7.2 Hz, 6H), 2.52 (m, 2H), 3.53 (d, J= 8.4 Hz, 2 H), 7.00 -7.40 (m, 10 H); min 2: -0.28 (s, 18H),1.10-1.20 (m, 6H), 3.03 (m, 2H), 3.77 (d, J= 8 Hz, 2H), 7.00-7.40 (m, 10H); min 3: -0.01 (s, 18H), 1.26 (d, J= 6.8 Hz, 6H), 3.11 (m, 2H), 3.82 (d, J= 7.2 Hz, 2H), 7.00-7.40 (m, 10H); *$^{13}C$ NMR*: ($CDCl_3$) for min 1 and min 3 isomers only: δ min 1: -0.04, 17.95, 41.72, 80.41, 125.71, 127.65 , 128.30; min 3: 0.40, 18.94, 42.59, 80.78, 126.24, 128.26, 128.67; *GC MS* (12 ev EI): m/e (intens.) min 1: 309.2 ($M^+$-105.2, 37.8), 220.2 ($M^+$-194.2, 4.4), 207.2 ($M^+$-207.2, 100.0)

**Desilylation of alkyl disilyl ethers (1,2-*bis*(cyclohexyl)-1,2-ethanediol(7))**

A mixture of the *dl/meso* pinacol *bis*-silylether (0.067 mmol), methanol (8 ml), 1 N HCl (4 ml), and THF (10 ml) was stirred at 20 °C for 5 to 6 h while monitoring by TLC. After rotary evaporation of the organic solvents, the resulting aqueous phase was extracted three times with ethyl acetate (3 x 8 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 ml) and then with brine (10 ml). The organic phase was dried over $Na_2SO_4$, concentrated, and flash chromatographed (4:1 petroleum ether/ether) to afford the diol.

*(1,2-bis(cyclohexyl)-1,2-ethanediol)*

yield: 66%; *dl:meso*: 2:1; *$^1$H NMR* ($CDCl_3$) δ maj: 0.95-2.12 (m, 11H), 3.32 (s, 2H); min: 0.95-2.12 (m, 11H), 3.42 (s, 2H);

## Preparation of authentic *dl* and *meso* samples of 1,2-bis(cyclohexyl)-1,2-ethanediol[16]

*dl*-Hydrobenzoin or *meso*-hydrobenzoin (1.00 g, 4.67 mmol), rhodium on alumina (5%; 0.05 g), and methanol (5 ml) were combined in a Fischer-Porter bottle. The system was flushed 3 times at 50 psi with $H_2$ and then was filled to 100 psi with $H_2$ to perform the reaction. The reaction mixture was stirred for 36 h under hydrogen pressure. The temperature was kept at 60 °C. After 36 h, the vessel was vented and the reaction contents were combined with 50 ml of ether and were filtered through celite with the aid of a water aspirator. The collected material was concentrated. The crude product was purified using flash chromatography. The column was initially eluted with ether and then with 4:1 petroleum ether/chloroform. The latter solvent system was collected and concentrated to yield a white solid.

*dl and meso 1,2-bis(cyclohexyl)-1,2-ethanediol*

*dl* yield: 88.2%; *$^1$H NMR* ($CDCl_3$) δ *dl*: 0.95-1.98 (m, 22H), 3.32 (d, 2H); *meso* yield: 85%; *$^1$H NMR* ($CDCl_3$) δ *meso*: 0.95-1.98 (m, 22H), 3.42 (s, 2H)

Published data corresponded with the above $^1$H NMR spectrum.[17]

## Silylation of cyclohexylmethanol (to 8)[23]

Dry THF (20 ml) and cyclohexylmethanol (24.4 mmol, 3.0 ml) were combined in a flask under nitrogen. Next, TMSCl (26.0 mmol, 3.3 ml) followed by triethylamine (26.0 mmol, 3.6 ml) were added to the reaction flask by syringes. The addition of the amine generated heat, white smoke and a precipitate. The reaction stirred at room temperature for

8 h and was monitored by TLC. Additional THF was added to help facilitate stirring. After stirring, water was added to the reaction flask and the aqueous layer was extracted with ether several times. The combined ether layers were washed with brine, dried over $Na_2SO_4$, and concentrated.

*Trimethylsilyl-cyclohexylmethyl ether*

Yield: 21% ; *$^1H$ NMR* ($CDCl_3$) 0.51 (s, 9H), 0.8-2.0 (m, 11H), 3.32 (d, J =7 Hz, 2H)

## Control reactions with various metal reducing agents

The metal [(Zn (activated and unactivated): 1.2 mmol, 0.144 g; or Mn: 1.2 mmol, 66 mg; or Al (activated): 3.0 mmol, 81 mg)] was combined with 15 ml of THF under nitrogen. TMSCl (2.2 mmol, 0.28 ml) and cyclohexanecarboxaldehyde (2.0 mmol, 0.24 ml) were added by syringe to the reaction flask. The mixture stirred for 24 h at ambient temperature and was monitored by G.C.

## Preparation of activated Al(Hg)[19]

Water (150 ml) was gently heated while nitrogen gas was bubbled through it for 30 min. Next, one scoop of $HgNO_3$ was added to the water. This solution became pale yellow and had a considerable amount of precipitate in it. The solution was cooled to room temperature. Aluminum foil (0.975g, 0.036 mol) was cut into one $cm^2$ pieces and weighed into a flask that was placed under nitrogen. The cooled $HgNO_3$/water solution was added to the flask containing aluminum. The mixture was stirred for 5 min; then, the water was removed using a syringe. Dry THF was used to wash the aluminum metal, and was inserted and removed from the flask using a syringe. The Al(Hg) was dried under vacuum. No yield was determined or analysis performed because of the high reactivity (possible decomposition) of the activated aluminum.

**Preparation of activated zinc metal**

Zinc metal (3.6 mmol, 0.24 g) was combined with 1M HCl in a round bottom flask under nitrogen. The mixture was stirred at ambient temperature for a few minutes, then the aqueous acid was canulated out of the reaction flask. The zinc remaining in the flask was washed with deionized water (20 ml), distilled THF (30 ml), and distilled diethyl ether (30 ml). The washings were added to the zinc using syringes and were removed through the canula. After the diethyl ether washing was removed, the zinc was dried under vacuum and stored under nitrogen.

**Reactions evaluating different catalysts**

The metal (1.2 mmol) was combined with the pre-catalyst (0.20 mmol) in a round bottom flask with side arm under nitrogen. Dry THF (15 ml) was added by syringe to the reaction vessel. The contents were allowed to stir from 15 to 30 min. Next, TMSCl (2.2 mmol, 0.28 ml) was added followed by cyclohexanecarboxaldehyde (2.0 mmol, 0.24 ml). The reactions were allowed to stir from 48 h to 4 or 5 days. All reactions were monitored by G.C. to evaluate the ratio of aldehyde to product (2,4,5-tricyclohexyl-1,3-dioxolane and/ or 1,2-*bis*(trimethylsiloxy)-1,2-dicyclohexylethane (4)).

*1,2-bis(trimethylsiloxy)-1,2-dicyclohexylethane (4)*

Characterized earlier in this section

*2,4,5-tricyclohexyl-1,3-dioxolane*

*$^1H$ NMR ($CDCl_3$) $\delta$ dl* isomer: 0.8-1.9 (m, 33H), 3.18 (dd, J= 6 Hz, 8.7 Hz, 1H), 3.34 (dd, J= 6 Hz, 9 Hz, 1H), 4.08 (d, J= 7.5 Hz, 1H); *meso* 1: 0.8-1.9 (m, 33H), 3.58 (d, J= 5.4 Hz, 2H), 4.41 (d, J= 7.2 Hz, 1H); *meso* 2: 0.8-1.9 (m, 33H), 3.64 (d, J= 5.7 Hz, 2H), 4.61 (d, J= 4.8 Hz, 1H); *GC/MS 12ev EI* m/e (intensity): 319 ($M^+$-1, 1.6), 237 ($M^+$-83, 85.2), 208 ($M^+$- 112, 17.4), 192 ($M^+$-128, 117), 109 ($M^+$-211, 95.0)

### Preparation of *Rac*-Ethylene-*bis*(4,5,6,7-tetrahydro-1-indenyl) titanium dichloride (Brintzinger's Catalyst) (12)[29]

*Rac*-ethylene-*bis*(indenyl)titanium dichloride (2.68 mmol, 1.00 g) was combined with $PtO_2$ (10% on carbon, 0.27 mmol, 61 mg), and freshly distilled DME (30 ml) in a stainless steel high pressure vessel. The vessel was pressurized (1500 psi) with hydrogen gas and stirred for 2 days at room temperature. After venting, the heterogeneous solution was filtered and washings were performed with ether. The filtrate isolated was concentrated to a red solid.

*Brintzinger's Catalyst*

yield: 65.4%; *$^1$H NMR ($CDCl_3$) δ dl* isomer: 1.4-1.6 (m, 4H), 1.8-2.0 (m, 4H), 2.3-2.4 (m, 2H), 2.5-2.6 (m, 4H), 3.0-3.2 (m, 6H), 5.55 (d, J=3 Hz, 2 H), 6.58 (d, J=3 Hz, 2H); *meso* isomer: 1.45-1.65 (m, 4H), 1.9-2.2 (m, 4H), 2.2-2.5 (m, 4H), 2.5-2.7 (m, 2H), 3.0-3.2 (m, 6H), 6.29 (d, 2H), 6.44 (d, 2H)

The NMR data was comparable to the published data.[29]

### Synthesis of ($\eta^5$-Cyclopentadienyl) titanium trichloride[32]

*Bis*-(Cyclopentadienyl) titanium dichloride (8.0 mmol, 2.0 g) and titanium tetrachloride (16.0 mmol, 1.74 ml) were combined in a Fischer Porter bottle under nitrogen. The black, thick mixture was heated between 130°C-150°C for 30 h. Next, the apparatus was connected to the vacuum line and the excess titanium tetrachloride was removed under vacuum. The remaining black solid was ground up using a mortar and pestle. After grinding, the black solid had the presence of some yellow solid in it. Purification can be performed by two different methods. First, sublimation of the black solid yields yellow crystals (yield: 64%). Second, trituration of the black solid with toluene yields some crude yellow product. A recrystallization of the yellow material using toluene and hexane added dropwise will allow more impurities to fall out of solution. The solution is filtered through Celite and the collected filtrate is concentrated to a yellow solid. Finally, this yellow solid is triturated with ether. The yellow residue remaining in the flask is $CpTiCl_3$ in its purest form.

*($\eta^5$-Cyclopentadienyl) titanium trichloride*

Yield: 64% (after sublimation); *$^1H$ NMR* ($CDCl_3$) δ 7.04 (s, 5H)

**Synthesis of di-*tert*-butylcyclopentadiene (1,3-, 1,4-, and 2,5-)**[30,31]

"Cracked" cyclopentadiene (0.029 mol, 1.89 g), t-butyl-bromide (0.143 mol, 16.4 ml), Adogen 464 (1.00 g Adogen/1.00 mol of KOH, 1.14 g), and 50% aqueous KOH (64.0 g KOH and 64.0 g $H_2O$) were combined in a flask and heated to 60°C for 1 h and 15 min and then to 100°C for 45 min. Vigorous stirring was necessary due to the viscous nature of the Adogen 464. The mixture was allowed to cool and pentane (20 ml) was added. The pentane layer was washed with water (10 ml) as well as a brine solution (10 ml). The organic layer was dried over $Na_2SO_4$ and concentrated to a black oil. Flash chromatography was used to purify the crude product with petroleum ether as the eluent. The material collected from the column was concentrated to a yellow oil.

*di-tert-butylcyclopentadiene (2 isomers)*

Yield: 42.1%; *$^1H$ NMR* ($CDCl_3$) δ isomer 1: 1.13 (s, 9H), 1.15 (s, 9H), 2.88 (s, 2H), 5.76 (s, 1H), 5.99 (s, 1H); isomer 2: 1.15 (s, 18H), 2.88 (s, 2H), 6.16 (s, 2H); *GC/MS* (12 ev EI) m/e (intensity): 178 ($M^+$, 67.9), 163 ($M^+$-15, 44.1), 121 ($M^+$-57, 16.2), 91 ($M^+$-87, 0.5), 57.2 ($M^+$-121, 100).

### Synthesis of *bis*($\eta^5$-1,3-di-*tert*-butylcyclopentadienyl)titanium dichloride (13)[30,31]

1,3-Di-*tert*-butylcyclopentadiene (5.62 mmol, 1.00 g), DME (3 ml), and benzene (6 ml) were combined in a flask under nitrogen at ambient temperature. n-Butyl lithium (1.6 M in hexanes, 6.18 mmol, 3.86 ml) was added to this solution dropwise. The solution was allowed to stir for 2 h after the addition of the base, and its color changed from a dark yellow to orange. Next, titanium tetrachloride (2.81 mmol, 0.309 ml) in hexane (6 ml) was added dropwise to the solution at 0°C. The solution became dark red as well as cloudy and had some precipitate present. After 30 min of stirring, chloroform (10 ml) and 6M HCl (5 ml) were added. The water layer was removed and the organic layers were concentrated. The oily sludge was rinsed with pentane until the pentane washings were pale yellow. The remaining solid was recrystalized using benzene and yielded orange-red crystals.

*bis($\eta^5$-1,3-di-tert-butylcyclopentadienyl)titanium dichloride*

Yield: 5%; *$^1$H NMR* ($CDCl_3$) δ 1.26 (s, 36H), 6.11 (d, J = 2.4 Hz, 4H), 6.65 (t, 2H)

The NMR data was comparable to the published data.[30,31]

### Synthesis of ($\eta^5$-di-*tert*-butylcyclopentadienyl)($\eta^5$-cyclopentadienyl) titanium dichloride (14)

($\eta$5-Cyclopentadienyl) titanium trichloride (2.36 mmol, 0.517 g) was combined with distilled THF (10 ml) and stirred under nitrogen at room temperature. In a separate flask, di-*tert*-butylcyclopentadiene (2.36 mmol, 0.420 g) was combined with THF (10 ml) and n-butyl lithium (1.6 M in hexanes, 2.36 mmol, 1.48 ml) and stirred for 2 h. The $CpTiCl_3$/THF solution was added dropwise to the solution containing the lithium salt. The resulting solution was heated to the reflux temperature of the solvent overnight. Next, the solvent was removed using the rotovap. The remaining residue was triturated with 1:1 methylene chloride and benzene. A white solid precipitated and a red liquid was removed and concentrated to a red solid. Additional purifications by flash chromatography using 3:1 petroleum ether: ether improved the purity of the product considerably.

*($\eta^5$-1,3-di-tert-butylcyclopentadienyl)($\eta^5$-cyclopentadienyl) titanium dichloride*

Crude Yield: 90%; *$^1$H NMR* ($CDCl_3$) δ: 1.25 (s, 18H), 6.54 (s, 2H), 6.58 (s, 5H), 6.90 (s, 1H); *$^{13}$C NMR* ($CDCl_3$) δ: 28.44 (6C), 113.06 (1C), 114.87 (2C), 117.54 (5C); *FAB 70ev* m/e (intensity): 360.1 ($M^+$, 5.6), 325.1 ($M^+$-35, 100), 295 ($M^+$-65, 28.6), 290 ($M^+$-70, 12.8), 275 ($M^+$-85, 2.6), 260.1 ($M^+$-100, 2.2), 245 ($M^+$-115, 3.0), 176 ($M^+$-184, 2.4)

**Reactions evaluating different recycling agents**

Manganese (1.2 mmol, 66 mg) was combined with $Cp_2TiCl_2$ (0.2 mmol, 50 mg) in a round bottom flask equipped with side arm under nitrogen. Distilled THF (15 ml) or distilled $CH_2Cl_2$ (15 ml) was added to the reaction vessel. The contents were stirred for approximately 15 min. Next, the recycling agent (2.2 mmol) was added followed by the aliphatic aldehyde (2.0 mmol).

**Preparation of collidinium chloride[33]**

A solution of collidine (0.051 mol, 6.8 ml) in butanol (27.2 ml) was treated with gaseous HCl which was generated by reacting $H_2SO_4$ (18 M, 0.13 mol, 7.1 ml) with NaCl (0.26 mol, 15 g). The HCl was bubbled into the collidine/butanol solution for approximately 5-6 h. White smoke was observed as well as the formation of a white solid. The flask containing the solid was placed in the refrigerator overnight to ensure maximum crystalization. The white crystals were collected by filtration and rinsed with butanol at -78°C, benzene at ambient temperature and then were dried.

*Collidinium chloride*

Yield: 14%; *$^1H$ NMR* ($CDCl_3$) δ 2.51 (s, 3H), 2.88 (s, 6H), 7.17 (s, 2H)

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# CHAPTER 4

# ENANTIOSELECTIVE PINACOL COUPLINGS

## Introduction and Background

### *Significance*

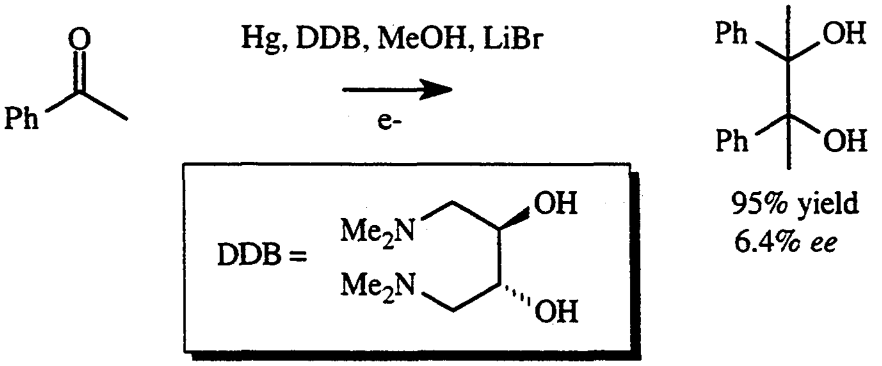
Generating chiral or non-racemic compounds for biological, chemical and medical purposes is a highly worthwhile area of research. Homochiral compounds can be obtained by asymmetric synthetic routes or from purification methods specifically designed to separate enantiomers. Although purification methods have been developed to separate enantiomers (e.g. chiral HPLC), asymmetric reactions that favor the production of one enantiomer over the other are more economically advantageous. Chirality can be incorporated into a reaction by changing one of the components required to perform the experiment from its achiral to a chiral form. This adjustment could be made on any material within the reaction such as a substrate, catalyst, or additive like a Lewis acid. For the purpose of this dissertation, chirality was present in the metallocene catalyst. Ideally, an asymmetric catalyst has the potential to produce multiple chiral product molecules from each chiral catalyst molecule. Because of this feature, chirality in the metallocene catalyst instead of one of the other necessary reagents offered the optimal approach. Moreover, metallocene complexes have another beneficial feature in that they can be readily designed with different ligands to alter both the electronic and steric environment of the catalyst. Tailoring a chiral catalyst opens up the possibilities for developing and optimizing catalytic, enantioselective reactions.

### *Literature Precedents*

Some prior work has indicated that enantioselective pinacolization is possible. These pinacolizations use both chemical and electrochemical means to induce enantioselective coupling of aromatic substrates. In all of these instances, homochiral additives or ligands are employed to produce moderate enantioselectivities.

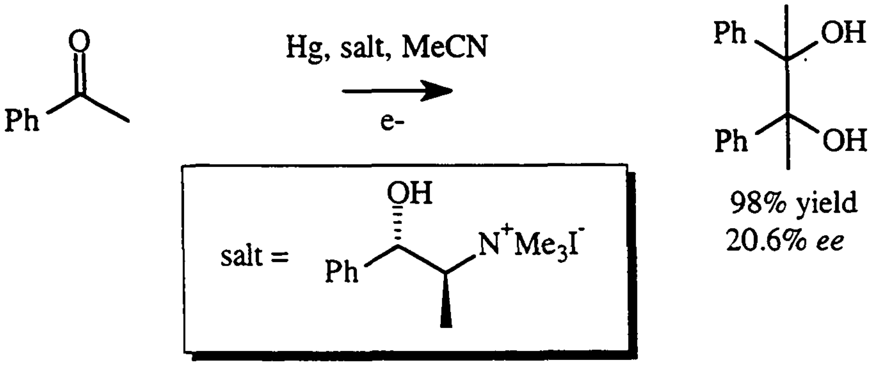
Seebach used a homochiral amine as an additive in the electropinacolization of acetophenone.[1] With the aid of the amine, some optical activity was observed (*ee* = 6%).

**Scheme 4-1: Enantioselective electropinacolization with homochiral amine**



Tilborg also used a homochiral, β-hydroxyamine additive to achieve enantioselectivity with the electropinacol reaction. With the use of this salt, an *ee* of 20.6% was achieved for acetophenone pinacolization.

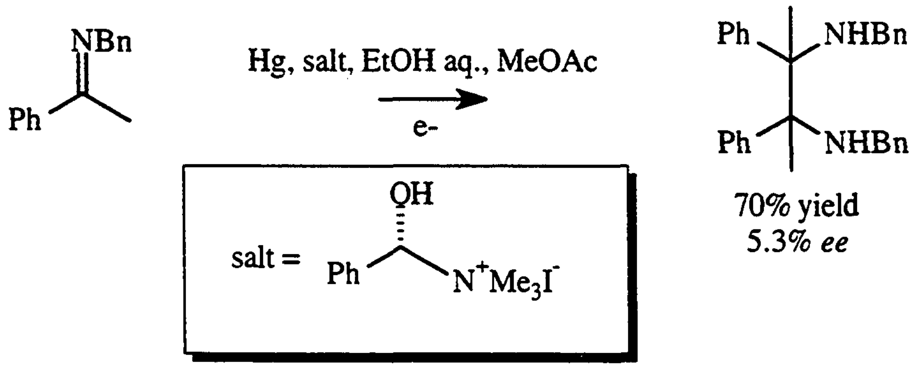
**Scheme 4-2: Enantioselective electropinacolization with homochiral β-hydroxyamine salt**



In both of these instances, stoichiometric amounts of mercury and a voltage of approximately -1.6 to -2.0 V were employed to perform the reductive coupling of the carbonyl substrates. Yields for both reactions were high (95 and 98% respectively); however, only a minor enantiomeric excess was produced in both of these reactions.

Enantioselective electropinacol coupling with imines has also been reported. An electron source, a stoichiometric amount of mercury, and a homochiral amine salt were used in the pinacolization. Horner reported a 70% yield for this coupling with a slight *ee* of 5.3%.[2]

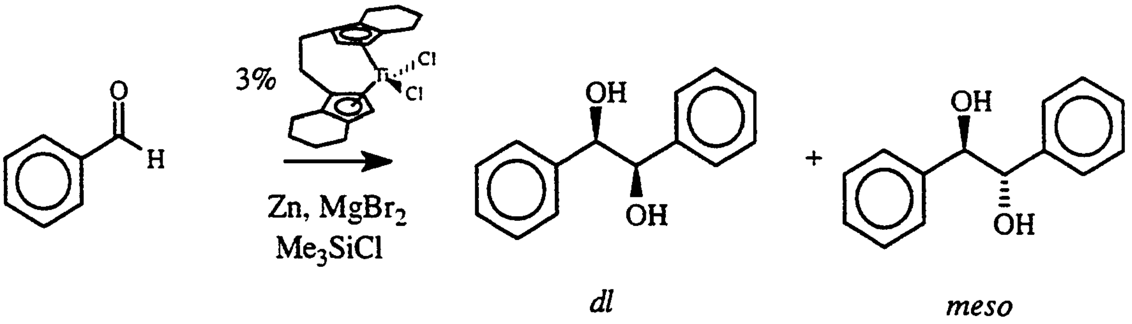
**Scheme 4-3: Enantioselective pinacolization of imines**



From these reports, it is clear that enantioselective pinacolization occurs when stoichiometric amounts of mercury in combination with an electron source and homochiral additives are employed. In these reported cases, limited enantioselectivity was achieved.

Little to no work has been performed on catalytic, enantioselective pinacol couplings. Gansauer performed reactions using racemic Brintzinger's catalyst on aromatic aldehydes.[3] He reported yields from 78 to 88% and *dl:meso* ratios from 96:4 to 98:2. Although Brintzinger's catalyst can be resolved, Gansauer did not report any pinacol couplings using the homochiral catalyst.

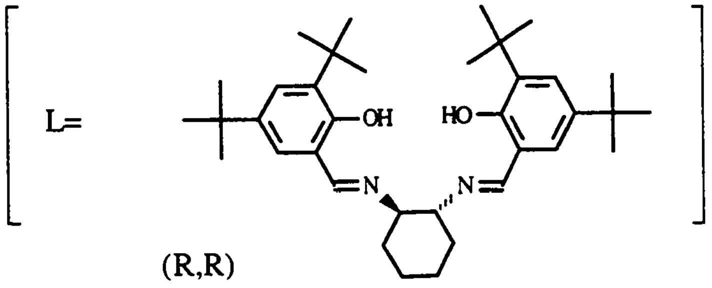
**Scheme 4-4: Pinacol coupling with rac-Brintzinger's catalyst**



Bandini performed enantioselective pinacol couplings using a chiral titanium-Schiff base complex.[4] The (R,R) ligand was reacted with $TiCl_4(THF)_2$ in acetonitrile to form the asymmetric catalyst *in situ.*

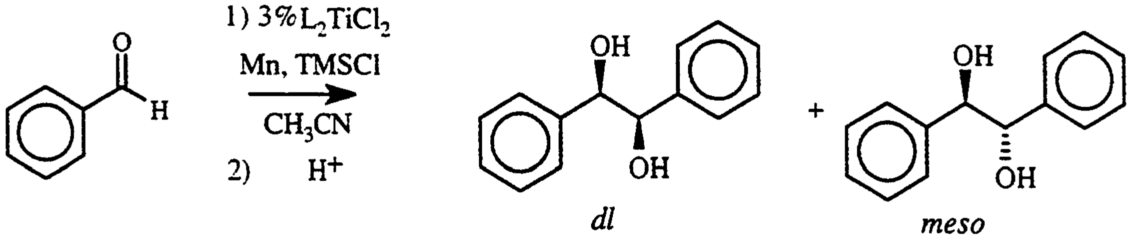
**Scheme 4-5: Asymmetric titanium-based Schiff catalyst**

$$2L + TiCl_4(THF)_2 \xrightarrow{CH_3CN} L_2TiCl_2$$



Pinacolization was carried out once the catalyst was generated. The reaction ran for approximately 24 hours and produced a 40% yield and a 90:10 *dl:meso* ratio. The enantiomeric excess was determined to be only 10%.

**Scheme 4-6: Chiral titanium Schiff-base catalyst coupling**



Although Brintzinger's catalyst was evaluated in racemic form, it can be resolved kinetically. Hence, resolving the catalyst would be a likely next step to determine if it can generate product enantioselectively. In the case of the asymmetric Schiff-base catalyst, enantiomeric excess was achieved. It should be noted that the enantioselective pinacol couplings achieved in the Nicholas laboratory preceded the one reported by Bandini. Bandini's work only further proved that asymmetric catalytic pinacol couplings were possible.

Several reports indicate that enantioselective pinacolization is possible. Both chemical and electropinacolizations have produced an enantioselective product. Homochiral amines present in the electropinacol reactions were responsible for the enantioselectivity that was achieved in the coupling of aromatic ketones and imines. Chemical methods ( e.g. chiral titanium complexes ) have also been employed to generate enantioselective pinacol products. Although moderate, the enantioselectivities presented to date indicate that selectivity is possible and worth further investigation.

## Results and Discussion

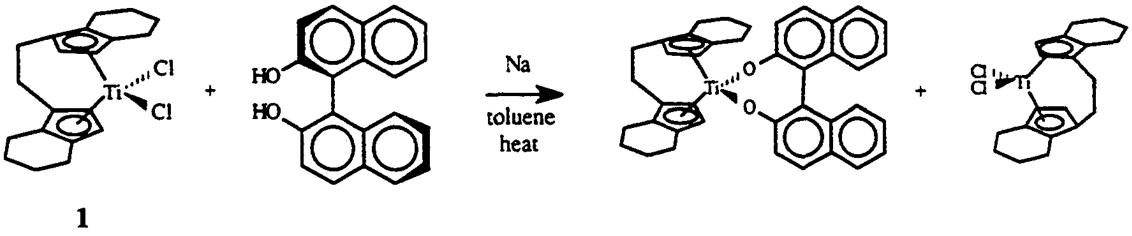
Five titanium-based complexes were tested in enantioselective pinacol couplings with benzaldehyde. Brintzinger's catalyst is commercially available and has been kinetically resolved in the Nicholas laboratory. The other four complexes were synthesized in both the Halterman and Glatzhofer laboratories with varying degrees of optical purity.

*Brintzinger's Complex*

Because it was commercially available, Brintzinger's catalyst was an ideal choice to evaluate for enantioselectivity. This *ansa*-metallocene was evaluated in racemic form with benzaldehyde using the optimal procedure discussed in chapter 2. The results indicated that *rac*-Brintzinger's catalyst was capable of inducing coupling of benzaldehyde with high yields (90%; aldehyde consumed based on G.C. chromatogram when reaction was halted) and selectively generating the *dl* isomer over the *meso* (7:1 *dl:meso* ratio).

Since Brintzinger's catalyst was capable of inducing pinacolization, its kinetic resolution was performed.[5]

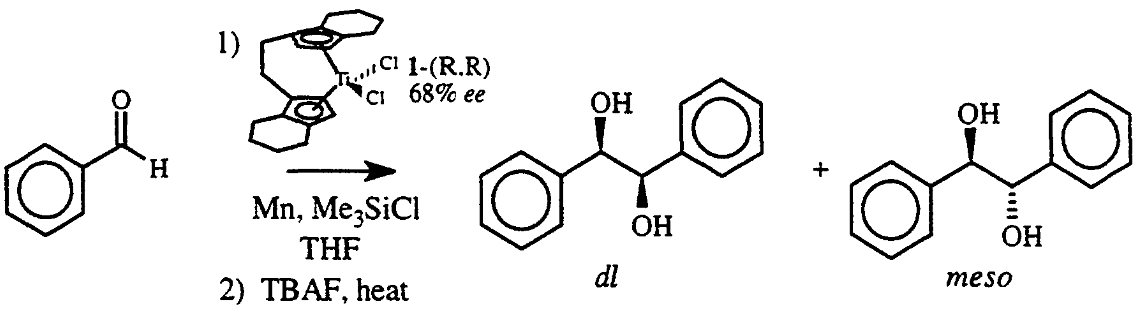
**Scheme 4-7: Kinetic resolution of Brintzinger's catalyst, 1**



The racemic complex was combined with homochiral (S)-(-)-binaphthol and sodium metal in toluene. The (S)-(-)-binaphthol reacts more quickly with the (S,S) enantiomer of Brintzinger's catalyst than the (R,R). When the reaction is stopped, the (R,R) form is free and the (S,S) form is converted to the binaphthoate. The latter is now chemically different than the free (R,R) enantiomer. The two compounds can be separated through chromatography at this point. With polarimetry, it was determined that the (R,R) enantiomer was isolated with an *ee* = 68%.

This enantiomerically enriched catalyst was used in a pinacol reaction with benzaldehyde using the standard procedure. The reaction ran for approximately 48 hours.

**Scheme 4-8: Coupling with homochiral Brintzinger's catalyst**

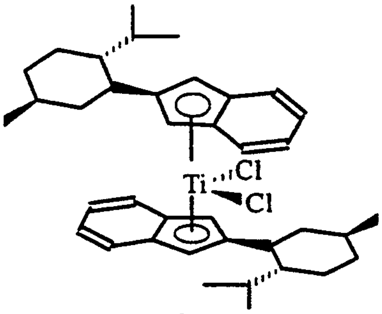


The resulting disilyl ether was hydrolyzed with TBAF/$H_2$0 to produce the diol. Flash chromatography was performed to separate the *dl* and *meso* diol isomers. Next, the chiral diol was evaluated polarimetrically and found to possess an enantiomeric excess of 60% (after correction for the catalyst with 68% *ee*). A description of the calculation performed can be found in the experimental section. It should be emphasized that in determining the *ee* value, it was assumed that only the bi- or trimetallic complexes possessing two RR Brintzinger enantiomers performed pinacolization; no cooperative effects were assumed to occur. Cooperative effects would include pinacolization by a *meso* bi- or trimetallic Brintzinger's intermediate (RR and SS enantiomer intermediate) and/or pinacolization by the other possible *dl* bi- or trimetallic intermediate (two SS Brintzinger enantiomers). This initial result with a chiral metallocene was very promising. Work with other asymmetric catalysts was pursued because of the success with Brintzinger's catalyst.

*Menthylindenyl titanium-based catalyst*

Three asymmetric catalysts synthesized in Dr. Ron Halterman's laboratory were also investigated in our pinacol reactions. Optically pure *bis*(2-menthylindenyl) titanium dichloride 2[6] was investigated with benzaldehyde using the standard procedure. Complex 2 has unique structural features that might enhance enantioselectivity. The complex does not contain a tether between indenyl groups as seen with other titanium complexes in this chapter. It does, however, possess bulky menthyl groups on the indenyl rings. The bulky groups are thought to force the complex to occupy one dominant conformation. The most thermodynamically stable conformation places the menthyl groups *anti* to one another. Rotation around the titanium-indenyl bonds is most likely restricted by the bulky menthyl groups, and the favored conformation will likely be the one in which the menthyl groups are *anti*. The reaction was halted after 48 hours when it appeared that the aldehyde was no longer being consuming (based on G.C.); the product:aldehyde ratio was 1:7.

**Figure 4-1: *bis*(2-menthylindenyl) titanium dichloride**



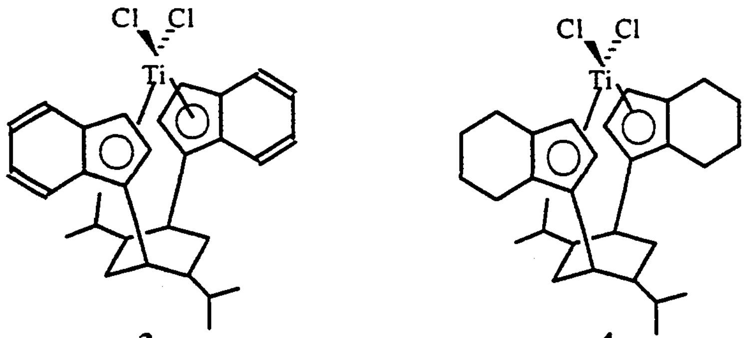
**2**

As for the selectivity of the reaction, the *dl:meso* ratio was 2:1. Flash chromatography was performed on the crude product to yield the purified disilyl ether. Next, desilylation was performed and the resulting *dl* and *meso* diols were purified through flash chromatography. Finally, the *dl* fraction was evaluated by polarimetry and indicated that the hydrobenzoin possessed an *ee* of 5.3%.

*Cyclohexyl tethered titanium-based complexes*

The remaining two catalysts were synthesized by Dr. Chengjian Zhu in Dr. Halterman's laboratory.[7] Each complex possessed a cyclohexyl group tether. (1S,7R,8R,10R)-2,5-Diisopropylcyclohexane-1,4-*bis*(1'-indenyl) titanium dichloride <u>3</u> was optically pure and (1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-*bis*(4',5',7',8'-tetrahydroindenyl) titanium dichloride <u>4</u> possessed an *ee* of 70%. Each catalyst was used in the standard pinacol coupling procedure (Mn, TMSCl, THF, ambient temperature) with benzaldehyde.

**Figure 4-2: Diisopropylcyclohexane-tethered catalysts**



3

4

Initially, the reactions with asymmetric catalysts 3 and 4 ran for 48 hours. However, G.C. analysis indicated that after 48 hours, acetal, along with unreacted aldehyde, was present instead of disilyl ether. Acid hydrolysis of the acetal could have produce the diol necessary for enantioselective evaluations. However, for purposes of consistency, the reactions using titanium-based catalysts 3 and 4 were repeated and halted after 24 hours when disilyl ether was still present. Disilyl ether was isolated from both of these reactions with some diastereoselectivity.

**Table 4-1: Benzaldehyde couplings using cyclohexyl-tethered titanium catalysts[a]**

| catalyst | product:aldehyde[b] | dl:meso[b] | %ee[c] |
|---|---|---|---|
| 3 | 1:3 | 4.6:1 | 0% |
| 4 | 1:4 | 3.4:1 | 32% |

[a] conditions: benzaldehyde, Mn, TMSCl, Ti-catalyst, THF, ambient temperature, 24 h; [b] product to aldehyde ratio determined when reaction was halted by G.C. and disilyl ether *dl:meso* ratio determined by G.C.; [c] *ee* for diol determined by chiral HPLC

The disilyl ethers in each reaction were desilylated using TBAF and then evaluated using chiral HPLC. It was discovered that the tetrahydro-titanium catalyst 4 produced an *ee* = 32% (after correction for catalyst with *ee* = 70%) while the *bis*-indenyl catalyst 3 afforded no enantioselectivity. Similar to Brintzinger's complex 1, the calculation for the *ee* resulting from complex 4 made certain assumptions. It was assumed that no cooperative effects were operating. Cooperative effects would include any other possible bi- or trimetallic intermediates that could have generated the pinacol product (e.g. RR and SS enantiomer of 4 forms a *meso* complex leading to *meso* isomer) and interfered in accurately determining the *ee* generated by the major enantiomer's bi- or trimetallic intermediate.

From the results of the four asymmetric catalysts evaluated, some generalizations were made. Brintzinger's catalyst 1 possesses an ethylene tether that made its structure somewhat more rigid relative to untethered metallocenes. It is reasonable to conclude that this inflexibility contributed to its ability to produce both a diastereoselective and enantioselective pinacol product. Catalyst 2 does not possess a tether, but instead used the presence of several bulky groups to reduce free rotation of the indenyl groups. Hence, this catalyst is also less flexible relative to some of the unsubstituted metallocenes. However, the stereoselectivity results achieved with catalyst 2 were negligible compared to the ones obtained with 1. These two catalysts indicate that the tethered system, in contrast to the sterically crowded one, provides better selectivity.

The results with catalysts 3 and 4, both possessing diisopropylcyclohexyl tethers, can also provide evidence for our hypothesis. This relative rigidity may be responsible for the diastereoselectivity obtained with each catalyst. The *dl:meso* ratios for 3 and 4 (approx. = 3.5:1) were not as high as observed with 1 (7:1); however, this could be attributed to the different structure of the tether used in catalysts 3 and 4. Also, some enantioselectivity was obtained with catalyst 4 which further indicates that tethered systems may influence stereoselectivity for pinacolization. The lack of enantioselectivity with catalyst 3 relative to catalyst 4 can be interpreted through electronic differences.

The electronic features of each catalyst may play a role in the rate of the reaction and selectivity. With Brintzinger's catalyst 1, the indenyl group was hydrogenated while it was not in 2. The reaction rates of these two experiments were quite different. In the case of 1, only trace aldehyde remained after 48 hours while in the reaction with 2, a significant amount of unreacted aldehyde was observed after several days.

The indenyl groups in complex 2 are somewhat electron withdrawing because of conjugation and could stabilize the titanium (III) species generated from reduction. The tetrahydroindenyl ligands in 1 lack this conjugation and therefore would be less likely to stabilize the titanium III complex resulting from reduction. The indenyl complex 2 therefore would be more readily reduced to its +3 state than the hydrogenated complex 1. However, once in the +3 state, complex 2 would not be as strong of a reducing agent as the +3 form of Brintzinger's, 1. The hydrogenated +3 form of Brintzinger's complex will be more electron donating than the +3 complex of 2. The low reactivity of 2 may be attributed to its failure to efficiently couple with the carbonyl substrate.

Catalyst 1 produced high enantioselectivity while catalyst 2 showed negligible selectivity. Because catalysts 1 and 2 differ greatly in both steric and electronic features, it is difficult to determine which factor affected enantioselectivity the most. The results with catalysts 3 and 4 indicate that electronics may in fact play a critical role in enantioselectivity. Complexes 3 and 4 differ only in the electronic character of the ligands. They possess indenyl and tetrahydroindenyl ligands respectively, but are identical in all other aspects.

Generalizations in regards to electronic features can be made when examining the results obtained from complexes 3 and 4. It should be emphasized that complex 4 produced some enantioselectivity while complex 3 did not. Complex 4, like Brintzinger's complex 1, possessed the tetrahydroindenyl ring system. Again, complex 3 which possesses indenyl ligands is more readily reduced than the tetrahydroindenyl complex 4. Once in the +3 state; however, complex 4 will be a more effective reducing agent than 3.

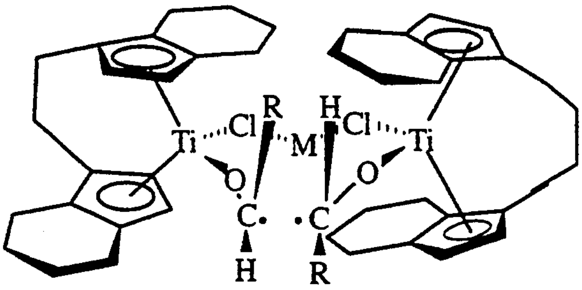
The increased reductive capability of 4 may allow it to coordinate to the carbonyl substrate more quickly.

In terms of transition states, it can be argued that the trimetallic intermediate formed from complex 4 may have a late transition state because of its increased reductive capability. In a late transition state, the carbon-carbon bond will be nearly formed. In contrast, it can be argued that with a trimetallic intermediate from complex 3 (because of its decreased reductive capability), an early transition state may be occurring in which the carbon-carbon bond is just beginning to form. In the early transition state model in which the carbon-carbon bond has not yet formed, the distance between the reactive carbon sites is greater; hence, there will be less steric hindrance present to favor one enantiomer over the other. In the late transition state with the trimetallic complex generated from 4, the carbon-carbon bond is almost formed, and the bond distance between the two reactive species is shorter. This shorter distance may increase the steric hindrance within the bi- or trimetallic intermediate and thus explain the higher enantioselectivity observed with titanium catalyst 4.

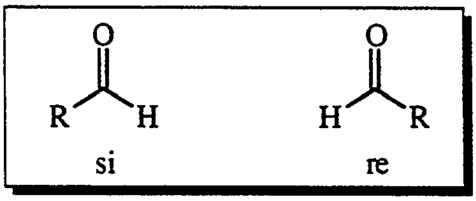
The explanation for improved enantioselectivity with tetrahydrodindenyl ligands is speculative. The results do suggest that catalysts with the tetrahydroindenyl ring system produce some enantioselectivity. Hence, when choosing additional catalysts for enantioselective pinacolization, tetrahydroindenyl ligands or ligands with similar electronic and steric features should be used.

The enantioselectivity achieved with some of these complexes can be rationalized through bi- or trimetallic intermediates. Since Brintzinger's catalyst, 1, produced the highest enantiomeric excess of all the complexes investigated, it is reasonable to use it to explain how enantioselectivity can be obtained. The S,S enantiomer of Brintzinger's complex is used to illustrate a potential trimetallic intermediate during the pinacol reaction.

**Figure 4-3: Trimetallic intermediate using S,S Enantiomer of Brintzinger's catalyst**



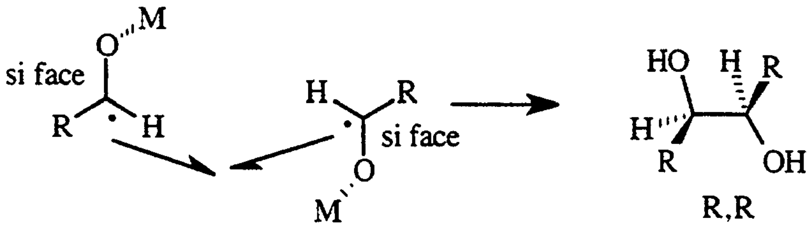
(si faces of carbonyl species form carbon-carbon bond)



In this intermediate, two S,S enantiomers coordinate to a metal such as Mn, Mg, or Zn. The S,S enantiomers arrange themselves in the lowest energy conformation. In this conformation, the cyclohexyl portions of each tetrahydroindenyl ligand are *anti* to one another. The carbonyl substrates coordinate to the titanium atoms and arrange themselves so that steric hindrance is limited. In this arrangement, the alkyl or aryl groups are *anti* to one another.

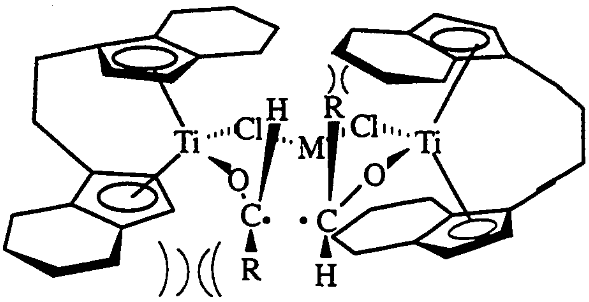
As described throughout this dissertation, an *anti* arrangement of the carbonyl's R groups leads to the *dl* isomers when an achiral titanium complex is used. When using homochiral complex 1, only one of the isomers (*d* or *l*) will be favored. In Figure 4-3, the carbon-carbon bond formation between the two carbonyl groups occurs from the *si* faces. The *re* faces of each carbonyl are facing the titanium complex. Through this arrangement, an enantioselective pinacol reaction is achieved and the R,R isomer of the diol is selectively generated (Scheme 4-11).

**Scheme 4-9: Formation of enantioselective pinacol product**



If the carbonyl groups were rotated so that the *re* faces reacted to form the carbon-carbon bond, the R groups would be closest to the sterically crowded portions of the titanium complexes.

**Figure 4-4: Disfavored trimetallic intermediate using S,S enantiomer of Brintzinger's catalyst**



(re faces of carbonyl species forming carbon-carbon bond)

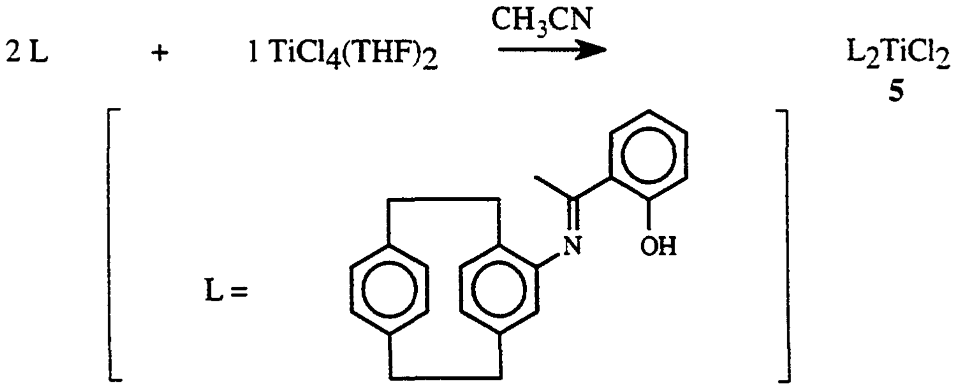
This particular conformation would be unlikely because of the steric hindrance produced. Since the carbonyl groups must form a carbon-carbon bond by reaction of both *si* faces, only one enantiomer, RR, can be expected with the S,S homochiral Brintzinger's trimetallic intermediate.

*Titanium Schiff-based catalyst*

One catalyst possessing paracyclophane ligands was investigated. The paracyclophane ligand was prepared in Dr. Dan Glatzhofer's laboratory and was 86.4%

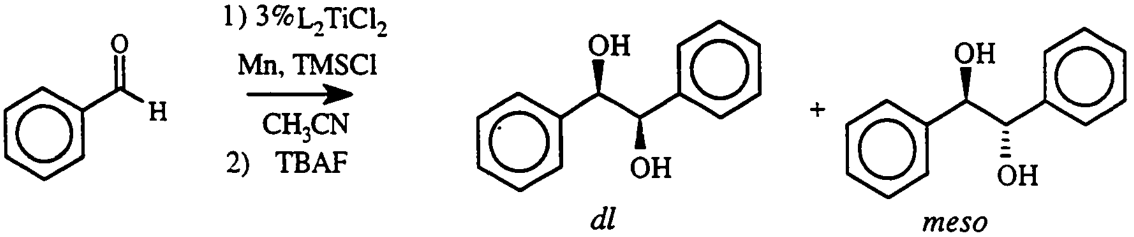
enantiomerically enriched.[8] This ligand was combined with $TiCl_4$-2THF to generate the enantiomerically enriched catalyst 5 *in situ.*

**Scheme 4-10: Generating optically pure titanium catalyst**



With the catalyst generated, the pinacol reaction was performed according to Bandini's procedure.[4] A solution of complex 5 was red but turned green after the reducing metal, manganese was added.

**Scheme 4-11: Chiral paracyclophane titanium Schiff-base catalyst coupling reaction**



The reaction ran for 48 hours until it was clear that aldehyde was no longer being consumed. Both disilyl ether and acetal were formed. Because of the limited amount of ligand available, the reaction was stopped at 24 hours as was done with reactions utilizing catalysts 3 and 4. G.C. analysis indicated that the ratio of combined products to starting aldehyde was 2:1 when the reaction was halted and worked-up. The *dl:meso* ratio in the case of the disilyl ether product was 1:1 while it was 10:1 in the case of the acetal. This change in selectivity from the disilyl ether to the acetal was observed in other reactions and will be elaborated on in chapter 5.

Desilylation was performed using TBAF and the resulting crude diol was analyzed with chiral HPLC. The *ee* produced by catalyst 5 was 3.7%. Unfortunately, the enantioselectivity with this new catalyst was negligible and further study was therefore not pursued.

## Conclusion

Five complexes were studied for potential contribution to an enantioselective pinacol reaction. Brintzinger's catalyst was the first complex investigated and produced high conversion of aldehyde to disilyl ether and a *dl:meso* ratio of 7:1. Moreover, a high degree of enantioselectivity was achieved with this particular catalyst. These initial results were encouraging and led us to evaluate other complexes that might have similar capabilities. Since the chirality we introduced in the reaction was from the metallocene catalyst, we investigated other metallocenes with distinctive steric and electronic features. Tethered systems as well as systems possessing sterically crowded groups were evaluated because of the limited rotation within the complex. Both indenyl and tetrahydroindenyl ligands were also examined in the complexes to study the effect of electronics in pinacol couplings. Enantioselectivity was achieved with some of these other catalysts. Titanium catalyst 4 produced the next highest *ee* relative to Brintzinger's catalyst 1, and catalysts 2 and 5 produced slight *ee* values. The catalysts most successful at enantioselective pinacol coupling possessed tethers connecting the ligands and tetrahydroindenyl rings. The tether more than likely contributed to a somewhat more rigid bi- or trimetallic intermediate that favored one enantiomer over another. The tetrahydroindenyl ligands probably contributed, through their electronic character, by production of a more reactive, chirally biased intermediate relative to metallocenes with indenyl ligands.

## Future Directions

The generalizations for optimal results will be used in choosing additional catalysts for *ee* pinacolizations Tetrahydroindenyl should be a primary ligand of interest: some variations on the alkyl ring portion for the ligand could be made to further investigate enantioselectivity. For example, the following ligands possessing various alkyl rings connected to the cyclopentadienyl ring could have similar success as catalysts using tetrahydroindene as a ligand.

**Figure: 4-5: Ligands for future enantioselective couplings**

Furthermore, in some of these additional ligands, the alkyl ring system possesses greater steric hindrance than that observed in the tetrahydroindenyl ligand. While this hindrance could decrease the likelihood of a bi- or trimetallic intermediate forming as was the case in other reactions, it could also provide enough steric crowding to favor one enantiomer over another.

Different tethers are also options for improving catalyst in enantioselective pinacolization. The two tethers shown to be successful included a ethylene tether and a diisopropylcyclohexyl tether. A variety of catalysts with different tethers would need to be evaluated to determine what type of tether would most effectively generate the enantioselective diol product. n-Alkyl tethers ranging from two to ten carbons have been prepared. Synthesis of catalysts with shorter tethers would have higher priority because of the more rigid nature the catalyst would possess. The longer tethered catalysts might lack the ability to produce a pinacol product selectively because of the increased flexibility within the complex. Other cycloalkyl groups are also possible tether candidates. Cyclopentanyl has been shown to bridge indenyl rings as a tether and would be the next likely candidate for a metallocene tethered by a ring. Finally, heteroatom tethers are also feasible for the project. Several silyl tethers have been observed and could influence the selectivity for enantio-pinacol reactions.

In summary, through our work with a variety of enantiomerically enriched or optically pure catalysts, we have proven that enantioselectivity can be achieved with catalytic pinacol couplings. Our initial result remained our optimal one; however, since some enantioselectivity was obtained with other catalysts, it is clear that further work in this area may eventually yield a catalyst more selective than Brintzinger's. Further probing of electronic and steric features with metallocene catalysts may allow more generalizations or trends to be made about what an effective catalyst is in the enantioselective pinacol reaction.

## Experimental

### *General Methods*

The majority of starting materials were commercially available. Brintzinger's catalyst was obtained in racemic form and was kinetically resolved for enantioselective purposes.[5] Three titanium-based catalysts were synthesized in Dr. Ron Halterman's laboratory. Optically pure *bis*(2-menthylindenyl) titanocene dichloride was synthesized by Jason Shipman; and, optically pure (1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-*bis*(1'-indenyl) titanium dichloride and (1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-*bis*(4',5',7',8'-tetrahydroindenyl) titanium dichloride in an enantiomeric excess of 70% were synthesized by Dr. Zhu. The enantiomerically enriched paracyclophane ligand used to synthesize the last titanium-based catalyst was prepared in Dr. Dan Glatzhofer's laboratory by Doug Masterson.[8] Tetrahydrofuran, and acetonitrile were distilled under nitrogen from sodium and benzophenone. Glassware was oven dried (125°C) and flushed with nitrogen before use. Liquids were transferred using syringes, and all solids were manipulated within the dry box.

$^1$H NMR and $^{13}$C NMR were obtained using a Varian XL-300 or a Varian Unity Inova-400 instrument. All NMR samples were dissolved in $CDCl_3$. A Hewlett Packard 5790A gas chromatograph and a Shimadzu GC-14A were used for monitoring reactions. GC/MS were obtained on a Hewlett Packard 5985 GC/MS instrument.

Gravity and flash chromatography techniques were employed. The silica gel used for gravity columns was 60 Å or 70-230 mesh, and the silica gel used for flash columns was 32-63 mesh. Petroleum ether, used in combination with diethyl ether for chromatography, was distilled to remove any high boiling impurities.

Polarimetry and HPLC techniques were utilized to evaluate enantioselectivity. An Autopol® III polarimeter was employed with some samples. HPLC work employed a 250x4.6 mm (L x I.D.) Chiralcel OJ column that was packed with cellulose *tris*(4-methylbenzoate) on 10 µm silica gel. The HPLC instrument included an SSI 222C pump and a Shodex RI-71 detector. The isopropyl alcohol and hexane used was degassed before being used for HPLC. Authentic samples of *dl* and *meso* hydrobenzoin were individually evaluated with HPLC before generated samples were injected onto the chiral column. The retention times for both enantiomers and the *meso* isomer were determined using these authentic hydrobenzoin samples.

## Resolution of Brintzinger's Catalyst[5]

*Rac*-ethylenebis-(4,5,6,7-tetrahydroindenyl) titanium dichloride (Brintzinger's catalyst) (0.50 g, 1.30 mmol) was weighed into a flask in the glove box. Dry toluene (60 ml) was added by syringe. Next (S)-(-)-binaphthol (186 mg, 0.65 mmol) was added to the reaction flask followed by sodium metal (0.22g, 10.0 mmol). The additions of binaphthol and sodium were added to the reaction flask outside of the dry box. A positive pressure of nitrogen was flowing through the reaction vessel at the time of both binaphthol and sodium additions to prevent any air from entering the reaction vessel. The solution was red with some precipitate. The mixture was stirred at 80°C for 4 h followed by stirring at ambient temperature for 1 h. The mixture was then filtered to remove sodium metal. The solution was purified using flash chromatography. The column was kept at -20°C. It was eluted first with 1:2 toluene: petroleum ether, second with 3:2 toluene: petroleum ether, and third with methylene chloride saturated with hydrochloride acid. The first fraction contained the (S,S) isomer-binaphthoate and the third fraction contained the free (R,R) isomer. The yield for (R,R) isomer was 54.2%. The enantiomeric excess of the isolated (R,R) titanium compound was determined by polarimetry.

*Brintzinger's catalyst (R,R)*

$^1$H NMR data can be found in the Experimental section of Chapter 3.

Published polarimetry data: concentration = $2.32\times10^{-4}$ g/ml in $CHCl_3$, $[\alpha]_D$ = 2440°, indicated 75% optical purity for (R,R) isomer.[5]

Data obtained in the Nicholas laboratory: $[\alpha]_{obs}$= +0.05°, c= $2.25\times10^{-5}$ g/ml in $CHCl_3$; therefore, $[\alpha]_D$ = 2200°; *ee*= 68%. The limited yield and thus low concentration of sample tested contributed to the small observed rotation determined (+0.05). This small observed rotation represents an area in which a significant amount of error may have been introduced.

### Standard Pinacol Coupling using catalysts 1-4

Chiral titanium catalyst (0.20 mmol) and manganese (50 mesh, 1.2 mmol, 66 mg) were added to a side arm round bottom flask under nitrogen. Distilled THF (20 ml) was added and the mixture was stirred for 15 min while changing from red to green. Chlorotrimethylsilane (2.2 mmol, 0.28 ml) was added by syringe followed by the aldehyde (2.0 mmol, 0.20 ml) and the mixture was stirred at ambient temperature for 24 to 48 h. Aliquots (approx. 0.5 ml) were removed while the reaction was in progress. The aliquots were filtered through Celite, dried under a stream of nitrogen, triturated with 4:1 petroleum ether:ether, and filtered through Celite again. Next, the aliquots were injected onto the G.C. to monitor the reaction progress. After 24 to 48 h, volatiles were removed by rotary evaporation, the residue was triturated with 4:1 petroleum ether/ether, and the washings filtered through celite. Concentration of the filtrate produced the crude products as orange or yellow oils. Further purification was accomplished by flash chromatography over silica gel using petroleum ether/ether as eluant providing the pinacol-*bis*-silyl ethers as colorless oils. The products were characterized by $^1$H NMR. Aldehyde was completely consumed only in the reaction using Brintzinger's catalyst.

*1,2-bis(trimethylsiloxy)-1,2-diphenylethane*

Spectral data can be found in Experimental section of Chapter 2.

*dl:meso* ratios obtained with each titanium-based catalyst:

*Brintzinger's (R,R) catalyst 1: dl:meso* = 7:1

*bis*(2-menthylindenyl) titanium dichloride (optically pure), 2 :*dl:meso* = 2:1

*(1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-bis(1'-indenyl) titanium dichloride 3: dl:meso* = 4.6:1

*(1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-bis(4',5',7',8'-tetrahydroindenyl) titanium dichloride* 4: *dl:meso* = 3.4:1

**Desilylation of 1,2-bis(trimethylsiloxy)-1,2-diphenylethane**

1,2-*bis*(Trimethylsiloxy)-1,2-diphenylethane (0.342 mmol, 116.2 mg) was combined with 10 ml of THF in a round bottom flask equiped with a water condensor. This solution stirred for a few minutes until the *bis*-silyl ether had dissolved. Next, tetrabutylammonium fluoride, TBAF, (1.0 M in THF, 0.3 ml; excess) was added *via* syringe. The solution became dark brown after this addition. The mixture was refluxed for 4 h. Next, the solution was cooled to ambient temperature and was quenched with 10 ml of water. The aqueous layer was extracted three times with diethyl ether. The organic layers were combined, dried over $Na_2SO_4$, and concentrated. The crude material was passed over a silica gel pipet column using ether as the eluent.

The hydrobenzoin isolated was examined for enantioselectivity by either the polarimetry or HPLC. When polarimetry was used, additional purification by either silica gel preparatory TLC or flash chromatography was performed on the samples to separate the *dl* and *meso* hydrobenzoin. The *dl* hydrobenzoin that was isolated was dissolved in methanol and analyzed by polarimetry. With HPLC, additional purification was not necessary since samples were injected on the OJ column. The flow rate was 1 ml/ min, and the eluent was 6% isopropyl alcohol in hexanes. Enantioselectivity was determined from HPLC.

*dl hydrobenzoin*

$^1$H NMR data can be found in Experimental section of Chapter 2.

Published data (Aldrich chemical catalog) for R,R hydrobenzoin: [$\alpha$] = +93°, *ee* = 100%

*Enantiomeric excess of hydrobenzoin achieved with different catalysts*

In catalysts that were enantiomerically enriched (not optically pure), it was assumed that no cooperative effects were occurring. No alternative bi- or trimetallic intermediate was being formed; only the intermediate from the major enantiomer is assumed to form.

*Brintzinger's (R,R) catalyst (68% ee), 1:* polarimetry: $[\alpha]_D = +38.6°$, *ee* = 61% ( 61 % *ee* corrected value based on *ee* of catalyst)

Calculation:

i.

$[\alpha]_{D\ \text{possible}} = [\alpha]_{D\ \text{known for hydrobenzoin}}$ x correction factor from *ee* of catalyst

$[\alpha]_{D\ \text{possible}} = (93°)(0.68)$

$[\alpha]_{D\ \text{possible}} = 63.24°$ (maximum rotation possible based on 68% *ee* of catalyst)

ii.

Corrected ee = 38.6°/63.24° x 100

= 61 % *ee* possible based on catalyst possessing only 68% *ee*.

*bis(2-menthylindenyl) titanium dichloride (optically pure), 2:* polarimetry: $[\alpha]_D = -6.11°$, *ee* = 5.3 %

*(1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-bis(1'-indenyl) titanium dichloride (optically pure), 3:* HPLC data: *ee* = 0 %

*(1S,7R,8R,10R)-2,5-diisopropylcyclohexane-1,4-bis(4',5',7',8'-tetrahydroindenyl) titanium dichloride (70% ee), 4:* HPLC data: *ee* = 32 % (32% is corrected value based on *ee* of catalyst)

Calculation:

$$\text{Corrected } ee = \frac{\text{RR enantiomer - SS enantiomer}}{\text{RR enantiomer + SS enantiomer } (0.70)} (100)$$

$$= \frac{2.24 - 1.42}{(2.24 + 1.42)\ (0.70)} (100)$$

$$= 32\%\ ee$$

*Numbers used for hydrobenzoin enantiomers (2.24 and 1.42 were peak areas observed in the HPLC chromatogram.

### Pinacol Coupling using enantiomerically enriched Schiff-base titanium catalyst (5)

The paracyclophane ligand (0.20 mmol, 70 mg)[8] was combined with $TiCl_4$-2THF (0.1 mmol, 33.4 mg) in a round bottom flask with side arm under nitrogen. Dry acetonitrile (7 ml) was added to this reaction vessel. This solution stirred for 30 min at ambient temperature. The temperature was then lowered to 0°C. Manganese (3.0 mmol, 170 mg) was added to the reaction mixture followed by TMSCl (1.10 mmol, 0.142 ml). After 5 min, benzaldehyde (1.00 mmol, 0.102 ml) was added by syringe. The temperature was allowed to rise to ambient temperature. The mixture was allowed to stir for 48 h and was monitored by G.C. Unreacted aldehyde was still observed when the reaction was halted. After 48 h, $NaHCO_3$ (3 ml) was used to quench the reaction. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 ml). The organic layers were combined and dried over $MgSO_4$ and then concentrated. The isolated disilyl ether was desilylated using the procedure with TBAF described earlier.

*1,2-bis(trimethylsiloxy)-1,2-diphenylethane*

Spectral data can be found in Experimental section of Chapter 2.

*dl:meso* ratios obtained with

*bis(2.2-paracyclophane) titanium dichloride (86.3% ee),* 5

*dl:meso* ratio for disilyl ether = 1.4:1

HPLC data for diol: *ee* = 3.7% (corrected value based on *ee* of catalyst)

For calculation format, see *ee* calculation for complex 4.

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# CHAPTER 5

# MECHANISTIC STUDIES

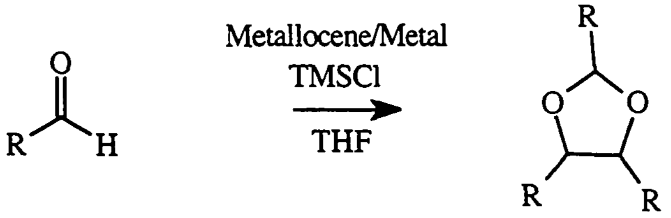
## Introduction and Background

The mechanistic studies performed during this project focused on addressing two questions about the inner workings of the catalytic pinacol reaction. First, in many of our experiments an acetal product was generated instead of the disilyl ether. This result was unexpected, and experiments were performed to determine the pathway by which acetal was formed. Second, it had been widely suggested that titanium reagents used in both stoichiometric and catalytic amounts produced highly stereoselective products through a trimetallic intermediate.[1-6] While this intermediate had been proposed, no definitive evidence was available to support its involvement. Our goal was to probe the nature of any intermediates involved in the $Cp_2TiCl_2$/Mn promoted pinacol reaction.

### *Acetal pathways*

In many of our experiments, acetal (Scheme 5-1, R= cyclohexyl or phenyl) was formed instead of disilyl ether. This result was unexpected, and at the same time interesting because the stereoselectivity for acetal formation was very high in several instances.

**Scheme 5-1: Acetal Formation**

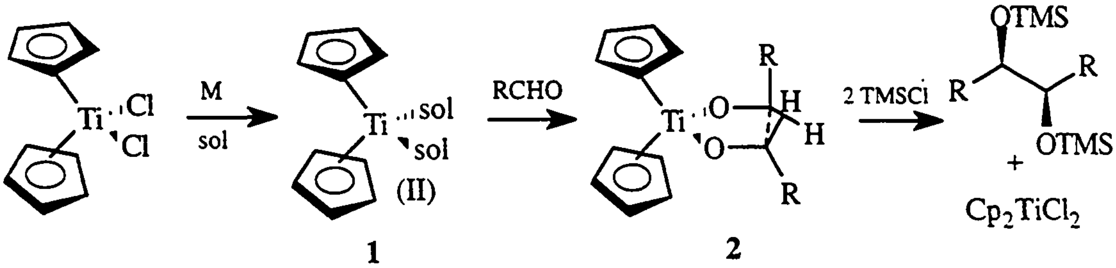


Two possible pathways were hypothesized to explain formation of acetal. One pathway suggested that disilyl ether was initially formed and was eventually converted into acetal. In the second pathway considered, both acetal and disilyl ether are formed independently of one another. The question of how acetal was formed was of interest to us and thus studies were designed to help answer this question.

*Mechanistic pathways via intermediates of different nuclearity*

In addition to a trimetallic intermediate, both mono- and bimetallic intermediates can be envisioned for the pinacol reaction. With the bi- and trimetallic intermediates, the metallocene dihalide is first reduced to the active +3 form by a reducing agent such as Zn, Mn, or Mg. The monometallic intermediate **1**, however, is produced in the +2 state. Once formed, the +2 species **1** (a two electron reductant) coordinates to two carbonyl substrates to form **2**. The carbon-carbon bond forms between the carbonyl fragments, and the recycling agent regenerates $Cp_2TiCl_2$ and forms the disilyl ether.

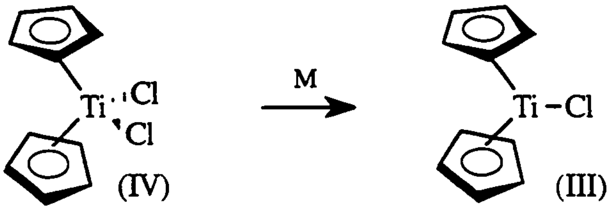
**Scheme 5-2: Monometallic intermediate in pinacol coupling**



The monometallic species **1** and **2** are unlikely intermediates in the pinacol reactions studied in our laboratory because titanocene dichloride must be reduced from +4 to +2. Reduction of titanocene dichloride to +3 using transition metals such as Zn, Mn, or Mg has been reported; however, no reduction to the +2 state has been observed under these mild conditions. Cases in which Ti (II) has been formed utilize either $CpTiCl_3/LiAlH_4$, $TiCl_4/Mg(Hg)$ or $TiCl_4/Zn$.[7-10] Both $TiCl_4$ and $CpTiCl_3$ are highly reactive relative to $Cp_2TiCl_2$, and the reducing reagents ($LiAlH_4$ and Mg(Hg)) are more powerful than the ones employed in our catalytic pinacol system. Furthermore, it has been reported that sodium amalgam is necessary to reduce titanocene dichloride to titanocene, $Cp_2Ti$ (II).[11] Based on literature precedents, it is unlikely that the titanium (II) species 1 and subsequently the monometallic intermediate 2 are formed in our pinacol reactions.

Two possible mechanisms lead to the suggested bimetallic intermediate 5. Both mechanisms involve the reduction of titanocene dichloride to its +3 state using a transition metal.

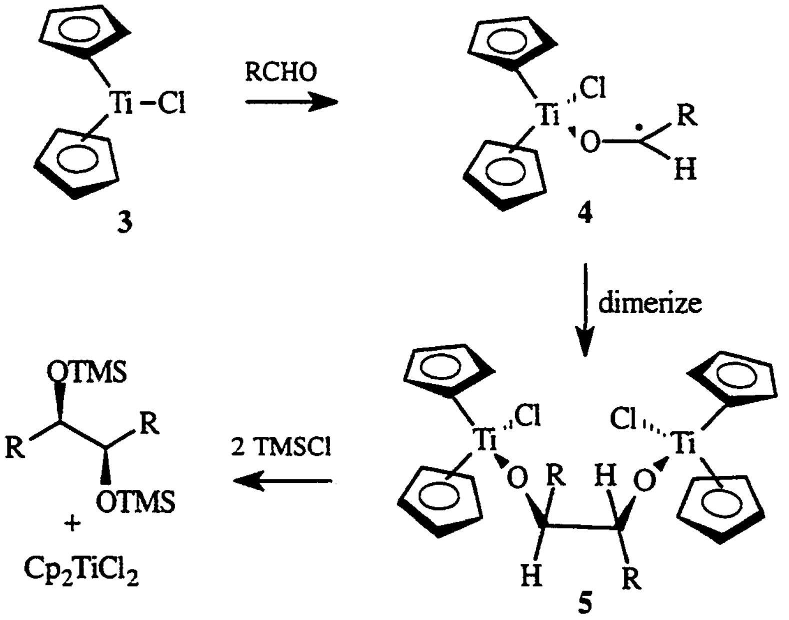
**Scheme 5-3: Formation of $Cp_2TiCl$**



3

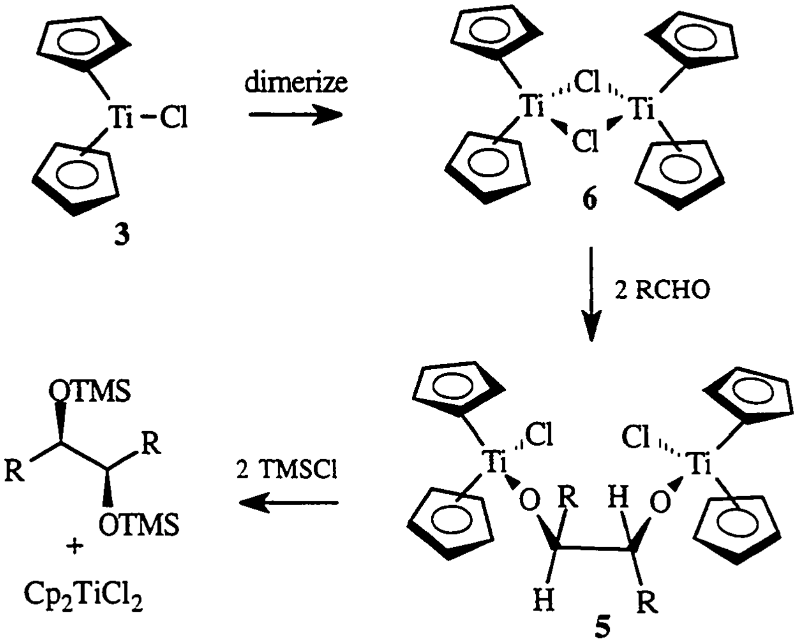
Once $Cp_2TiCl$ 3 is formed, two possible pathways can lead to the bimetallic intermediate 5. In pathway one (Scheme 5-4), $Cp_2TiCl$ coordinates to a carbonyl moiety to form 4. Dimerization of species 4 with itself forms the bimetallic intermediate 5. The carbon-carbon bond can then be generated and finally the product and $Cp_2TiCl_2$ are formed using TMSCl as a recycling agent.

**Scheme 5-4: Pathway 1 towards bimetallic species 5**



In the second pathway (Scheme 5-5), Cp$_2$TiCl dimerizes first to form the bimetallic species **6**.

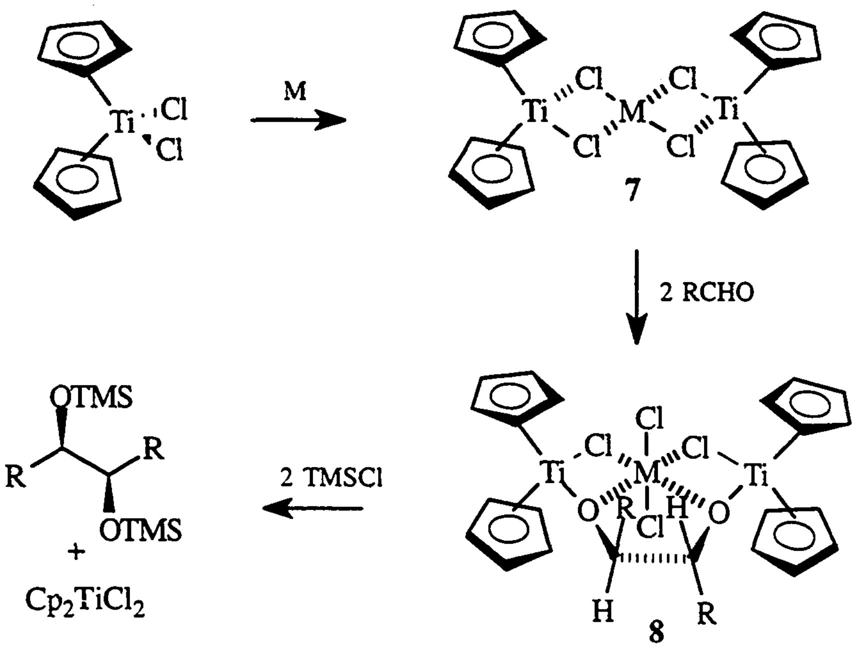
**Scheme 5-5: Pathway 2 towards bimetallic species 5**



Next, two carbonyl substrates coordinate to the titanium atoms in 6 to form the bimetallic moiety 5. With the carbonyl substrates coordinated in a close proximity to one another, carbon-carbon bond formation can occur. The TMSCl recycles the titanium reagent back to $Cp_2TiCl_2$ and the disilyl ether product is generated. Bimetallic intermediate 5 is formed in both pathways; however, the method by which 5 is generated differs with each pathway.

The trimetallic complex 7 incorporates the oxidized form of the metal reducing agent into its structure, essentially bridging the reducing metal between the two titanium atoms. Two carbonyl substrates coordinate to the titanium atoms to form 8. Then, TMSCl acts as a recycling agent to regenerate the titanocene dichloride and form the disilyl ether product.

**Scheme 5-6: Trimetallic intermediate in pinacol coupling**



A significant difference between bi- 6 and trimetallic intermediate 7 is the distance between the two titanium atoms. A greater distance exists between the titanium atoms in the trimetallic complex relative to the bimetallic complex. The differing distances between titanium atoms may have an important role in determining yields, reactivities, and selectivities. Once the carbonyl moieties coordinate to the complex, the distance between the titanium atoms influences the distance between the reactive carbonyl carbons. If the distance between the two reacting carbons is too large, the extent of carbon-carbon bond formation will be small and the amount of steric interaction between the carbonyl bulky groups (alkyl or aryl) will be limited. Without steric hindrance to enforce the *anti* arrangement of the bulky groups, lower diastereoselectivity will be achieved. It is also conceivable that the distance between the two titanium atoms in the complex may be too small. In this scenario, the titanium complex is too sterically hindered to allow the carbonyl species to coordinate to the titanium atoms. Without effective coordination, no pinacolization can occur. While the negative results from improper Ti-Ti distances has been noted, it should be emphasized that with a proper distance between titanium atoms in a complex, successful coordination of both carbonyl moieties can occur. Moreover, a certain amount steric hindrance can be envisioned to encourage stereoselective formation of products without preventing the initial coordination of carbonyl to metal. In summary, the distance between the titanium atoms in a complex may be critical not only for the formation of pinacol product but also for achieving high diastereoselectivity.

Bi- and trimetallic compounds (6 and 7 respectively) have been reported and were synthesized in the Nicholas laboratory. Pinacol reactions using stoichiometric amounts of 6 and 7 were performed to probe which intermediate (5 or 8) was operating in pinacolization. Kinetic studies were also performed in an effort to determine what the rate determining step was in the catalytic cycle. We hoped to determine the kinetic order of titanium in the reaction to further verify which intermediate was active in the pinacol coupling.

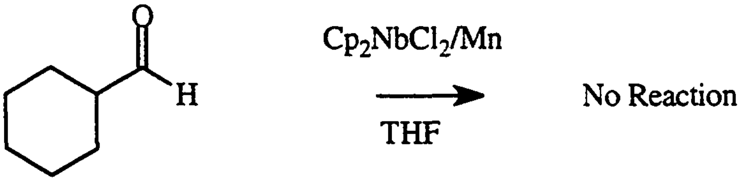
## Results and Discussion

A number of complexes, $Cp_2NbCl_2$, $Cp_2TiBr_2$, $(1,3\text{-t-bu}_2Cp)_2TiCl_2$, $(1,3\text{-t-bu}_2Cp)(Cp)TiCl_2$, and isopropylidene(fluorenylcyclopentadienyl) titanium dichloride, investigated in earlier chapters were shown to produce an acetal product instead of the disilyl ether product observed with $Cp_2TiCl_2$. This was the case with both aromatic and aliphatic aldehydes (benzaldehyde and cyclohexanecarboxaldehyde). Also, it was discovered that in some cases, the acetal *dl:meso* ratio achieved was very high. Various experiments were performed to determine the mechanism by which the acetal was formed.

### *Investigation of acetal formation*

Since the acetal product did not incorporate a portion of the TMSCl in its structure, it was hypothesized that this reagent may not play a role in the reaction. Hence an experiment was performed in which the silyl reagent was omitted.

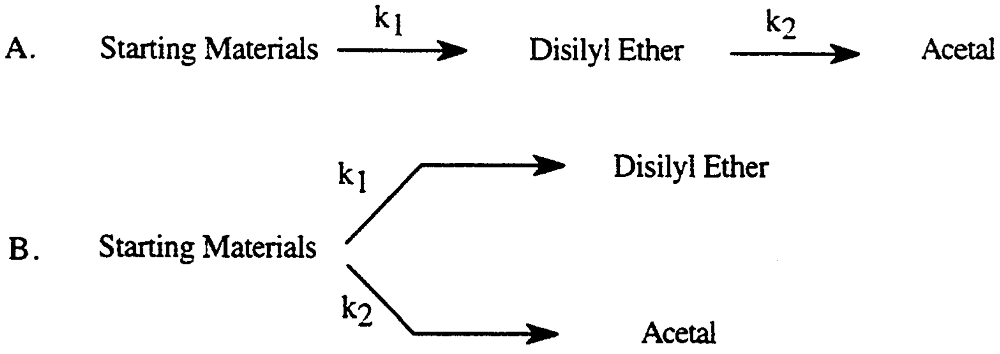
**Scheme 5-7: Reaction without TMSCl**



This reaction was run using a catalytic amount of $Cp_2NbCl_2$ (a catalyst for acetal formation) with manganese as a stoichiometric reducing agent. Cyclohexanecarboxaldehyde was the substrate and the medium was THF. After a period of 24 hours, no product of any kind was observed by G.C. analysis. From this experiment, it was clear that TMSCl played an important role in acetal formation.

The failure of the reaction without TMSCl was unexpected and forced us to re-evaluate previous results that had yielded acetal. Upon further analysis of G.C. chromatograms in which acetal was formed, it became apparent that early on in these reactions, a small amount of disilyl ether was being formed. However, after approximately 24 hours, the disilyl ether was either insignificant relative to acetal or completely absent from the G.C. chromatogram. Two possible mechanisms were hypothesized at this point:

**Figure 5-1: Pathways for acetal formation**

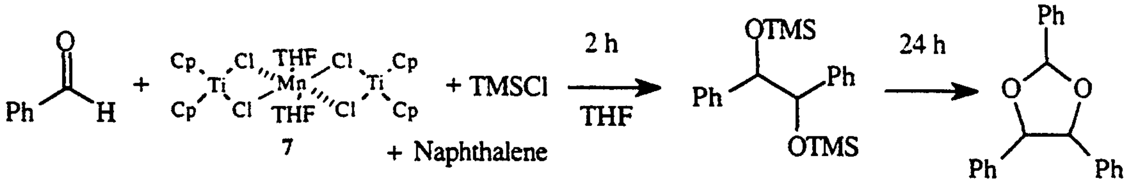


In pathway A, starting materials are initially converted to disilyl ether which, over time, are then converted into acetal. This pathway could explain why disilyl ether was seen after a few hours in G.C. chromatograms but was no longer present after approximately 24 hours (only acetal). Pathway B suggested that two competing reactions were operating and were independent of one another.

A reaction in which one product is consumed to produce another can be characterized by the concentration of products as a function of time. The concentration of disilyl ether relative to the concentration of acetal will not be constant as time progresses in pathway A. Pathway B can also be described in terms of product concentrations. When two reactions are occurring independently of one another, the concentration of disilyl ether relative to the concentration of acetal will be constant over time. The product concentrations will be beneficial in determining which mechanism is operating.

An experiment utilizing an internal standard was run to determine which pathway, A or B, was operating during pinacolization. The trimetallic compound 7 was chosen because earlier experiments suggested that it formed disilyl ether within two hours and acetal within 24 hours. With some of the other catalysts that formed acetal, only a trace amount of disilyl ether was formed early on. Compound 7 produced a significant amount of disilyl ether and acetal during the reaction and thus was a good candidate for the investigation. Naphthalene was chosen as an internal standard because of its chemical inertness in the pinacol reaction and because of its non-interfering retention time.

**Scheme 5-8: Investigation of acetal formation using internal standard**



The reaction components included benzaldehyde as the substrate, TMSCl, naphthalene, and a stoichiometric amount of the trimetallic complex 7 synthesized in the dry box. Because of the extreme air and moisture sensitivity of 7, the reaction was performed completely in the dry box. Aliquots were removed from the dry box and analyzed.

**Table 5-1: Disilyl ether and acetal formation**[a]

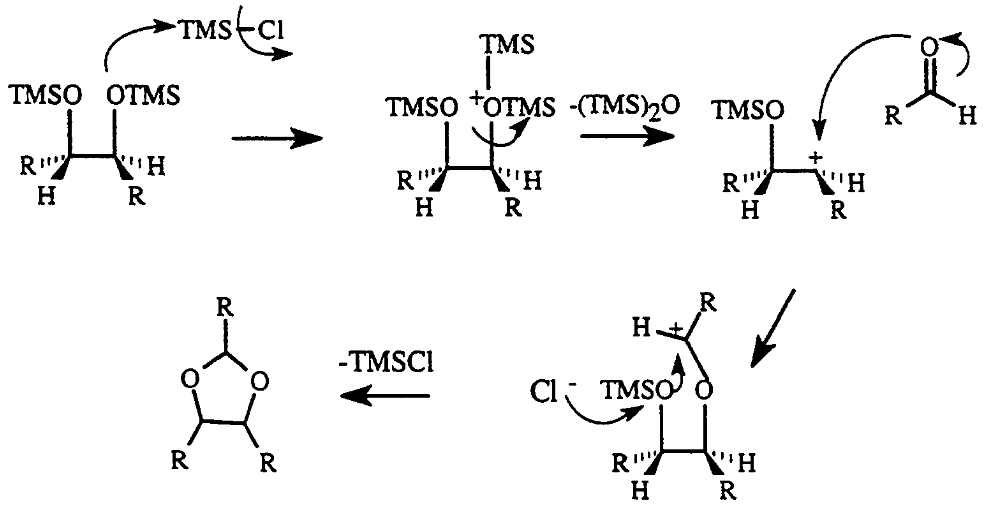
| Time | Aldehyde | disilyl ether | acetal | naphthalene |
|---|---|---|---|---|
| 5 min | 1.5 | 0.19 | 0 | 1 |
| 1 h | 1.6 | 0.40 | 0 | 1 |
| 24 h | 1.0 | 0 | 0.40 | 1 |

[a] Numbers in Table 5-1 represent peak areas taken from G.C. chromatograms.

The G.C. peak areas for disilyl ether and acetal were compared to the internal standard, naphthalene, at different times during the reaction. Based on the peak areas of products relative to naphthalene, disilyl ether was being converted into acetal after a period of several hours. The concentration of disilyl ether relative to acetal was changing with time (not constant); therefore, pathway A was operating. It should be noted that the disappearance of aldehyde did not correlate with the formation of product. Based on this additional observation, there is a possibility that acetal formation may not directly correlate with the consumption of disilyl ether. Further studies would be necessary to determine if an additional pathway towards acetal formation is operating.

The experiments using the naphthalene internal standard produced some insight into the mechanism of acetal formation. A mechanism is proposed below to interpret the observations.

**Scheme 5-9: Hypothesized mechanism for acetal formation**

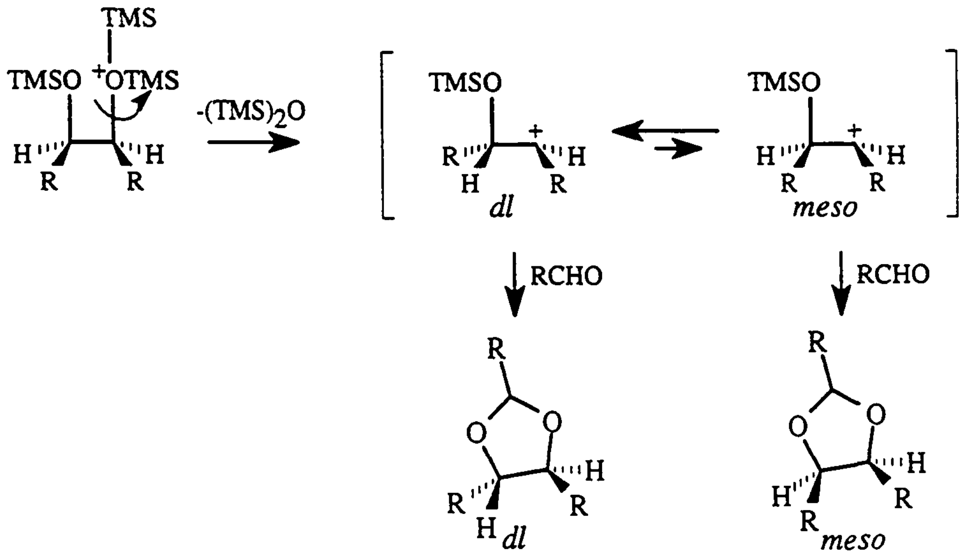


First, disilyl ether is formed through the catalytic pinacol reaction described throughout this dissertation. Once formed, the disilyl ether undergoes further reaction with TMSCl to eventually eliminate a *bis*-silyl ether and form a cation. This cationic intermediate reacts with a carbonyl species in the system to form another cation. Finally, chloride acts as a nucleophile to remove the remaining silyl group on the intermediate. TMSCl is generated and the acetal is formed.

Acetal was observed exclusively in some of the achiral metallocene-catalyzed reactions, particularly the slower ones. The suggested mechanism in Scheme 5-9 may provide an explanation for this observation. Pathway A (Figure 5-1) defines the rate of formation of disilyl ether as $k_1$ and the rate of formation of acetal as $k_2$. In the slower reactions, it is probable that $k_2>k_1$; thus, as soon as disilyl ether is generated, it is consumed and converted to acetal. Scheme 5-9 illustrates the consumption of disilyl ether with the reaction between disilyl ether and chlorotrimethylsilane that eventually leads to acetal. The other use for TMSCl involves its reaction with reductively coupled aldehyde to form disilyl ether. Since $k_2>k_1$, chlorotrimethylsilane will react more readily with the disilyl ether to generate acetal.

In some reactions, it was noted that low *dl:meso* ratios were observed with the initial disilyl ether formed, and high *dl:meso* ratios were found with the acetal that formed later in the reaction. Some speculation can be offered to interpret these results. As discussed in chapter 3, moderate *dl:meso* ratios for the pinacol coupling of aliphatic aldehydes were observed. This result was attributed to the steric and electronic features of the aliphatic aldehydes and was discussed in chapter 3. As for the high *dl:meso* ratio observed with the acetal, it can be interpreted in terms of the carbocation formed *via* elimination of *bis*-silyl ether (Scheme 5-10).

**Scheme 5-10: Selectivity for *dl* acetal**



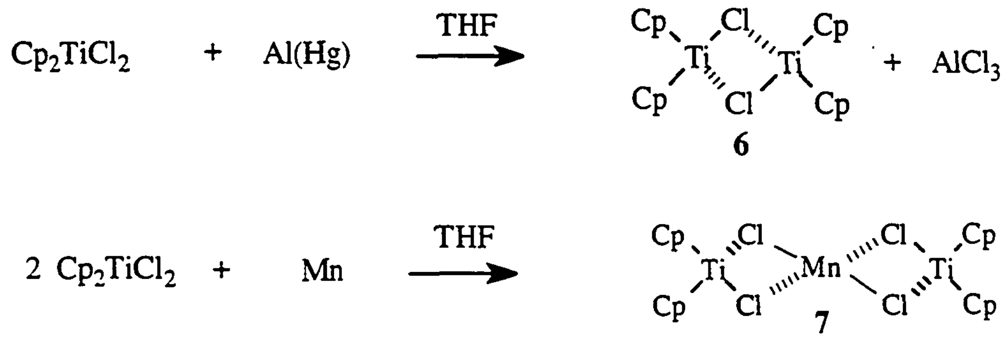
The carbocation exists in an sp$^2$ planar state. Free rotation around the carbon-carbon bond is possible and would allow the alkyl and hydrogen groups to occupy the most energetically stable position. This free rotation places the R groups *anti* to one another to minimize steric hindrance. Through this suggested mechanism, the high diastereoselectivity of acetals can be interpreted.

Some understanding of the mechanism was achieved through these studies. Thus, chlorotrimethylsilane plays an important role in the formation of disilyl ether as well as acetal. Also, it was discovered that disilyl ether was consumed and converted to acetal.

### *Comparison of bi- and trimetallic compounds 6 and 7*

Both bi- and trimetallic intermediates (5 and 8) have been suggested to explain the high diastereoselectivity achieved during stoichiometric and catalytic pinacolizations using titanium-based metallocenes. The preparation and characterization of bi- and trimetallic compounds 6 and 7 were reported by Coutts, Stucky, and Stephan.[12-14] Compounds 6 and 7 were synthesized in the Nicholas laboratory for the purpose of evaluating the role of the intermediates (5 and 8) during pinacol coupling.

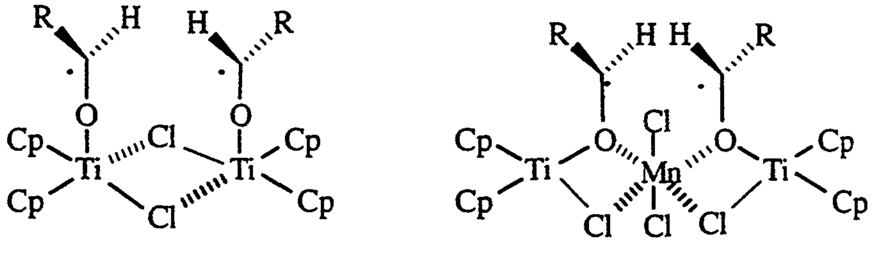
**Scheme 5-11: Synthesis of bi- and trimetallic complexes**



When preparing 6 and 7, all manipulations were performed in the dry box because both intermediates are extremely air and moisture sensitive.

Ideally, the bi- and trimetallic compounds (6 and 7) would react with carbonyl substrates to form intermediates (transition states) 5 and 8 as suggested in literature.

**Figure 5-2: Suggested bi and trimetallic intermediates**



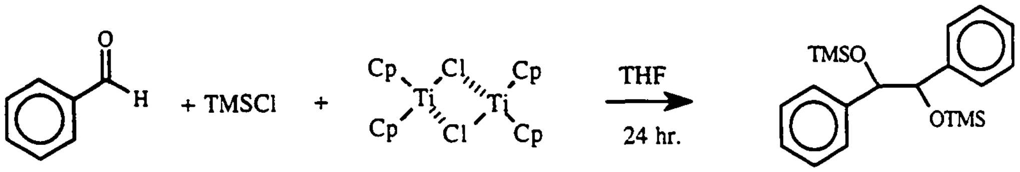
5

8

The bi- and trimetallic carbonyl intermediates (5 and 8) have been suggested as the structural feature responsible for high diastereoselectivity in pinacol reactions using stoichiometric amounts of titanium-based reagents.[3-5] As for the catalytic pinacolizations, only the trimetallic intermediate 8 has been proposed as an intermediate to account for the high *dl:meso* ratios. [1,2,6,15,16]

In our laboratory stoichiometric amounts of compounds 6 and 7 were each used in pinacol reactions. Bimetallic compound 6 was used in combination with benzaldehyde and TMSCl in THF. The reagents were combined and stirred in the dry box. Aliquots were periodically removed from the reaction and examined by G.C outside of the dry box.

**Scheme 5-12: Pinacolization using stoichiometric amount of bimetallic complex, 6**



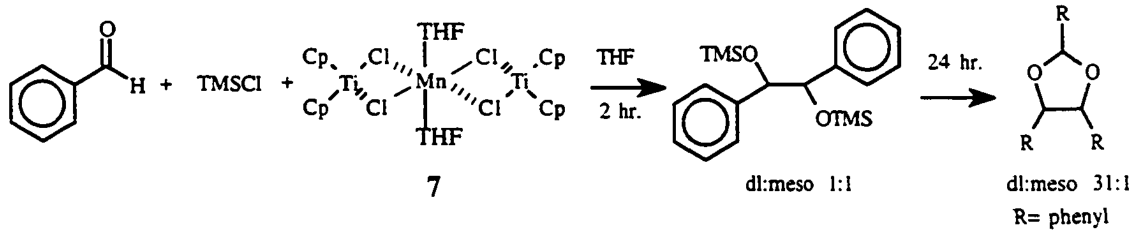
6

dl:meso 29:1

After approximately 24 hours, the aldehyde/disilyl ether ratio was 3:1. The disilyl ether's *dl:meso* ratio was 29:1. No acetal was observed after 24 hours and after four days, only trace amounts of acetal could be seen by G.C.

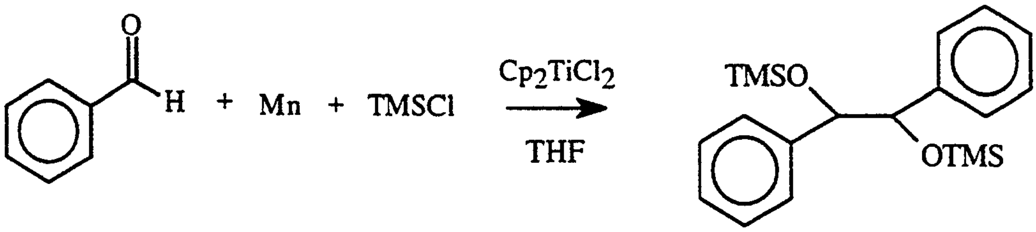
The trimetallic complex 7 was combined in stoichiometric amounts with benzaldehyde and TMSCl in THF. Similar to the bimetallic-mediated reaction, the reagents for the trimetallic mediated reaction were combined and allowed to react in the dry box. Aliquots were removed from the dry box and analyzed by G.C. The results obtained with this reaction were quite different than the ones seen in the reaction with the bimetallic intermediate. After a period of two hours, disilyl ether could be seen; however, the *dl:meso* ratio was 1:1. No diastereoselectivity was observed in this particular case. However, after 24 hours, no disilyl ether was observed by G.C. Acetal was the only product seen, and it possessed a *dl:meso* ratio of 31:1.

**Scheme 5-13: Pinacolization using stoichiometric amount of trimetallic complex,7**



The results using stoichiometric quantities of the bimetallic complex 6 (Scheme 5-12) are similar to the results achieved in the catalytic pinacol coupling of benzaldehyde using $Cp_2TiCl_2$/Mn (Scheme 5-14). In both reactions, disilyl ether was the product observed; no acetal was seen in either of these experiments. While both reactions produced a high *dl:meso* ratio, a significant difference between the two ratios was observed and warrants discussion. The catalytic reaction (13:1) showed a lower *dl:meso* ratio relative to the stoichiometric bimetallic reaction (29:1).

**Scheme 5-14: Standard catalytic pinacol coupling**



It was hypothesized that in the catalytic reaction, other metallocene intermediates (e.g. trimetallic 7), in addition to the bimetallic one proposed, may have induced pinacolization with a lower degree of diastereoselectivity. Gansauer argued that a less selective pinacol reaction mediated by titanium (III) alkoxides interfered with diastereoselectivity in some reactions.[17,18] These less selective intermediates, whether trimetallic 7 or titanium (III) alkoxides, may have caused the overall catalytic reaction to appear less selective (*dl:meso* ratio 13:1 instead of 29:1).

In the reaction using stoichiometric amounts of trimetallic complex 7 (Scheme 5-13), disilyl ether was observed by G.C. after 2 hours with a 1:1 *dl:meso* ratio; after 24 hours, no disilyl ether was observed, only acetal in a *dl:meso* ratio of 31:1. In contrast, the $Cp_2TiCl_2$-catalyzed pinacol reaction (Scheme 5-14) produced a disilyl ether with a *dl:meso* ratio of 13:1 after 24 hours. Based on these results, it can be concluded that the trimetallic complex 7 was not the primary product forming intermediate in the catalytic reaction.

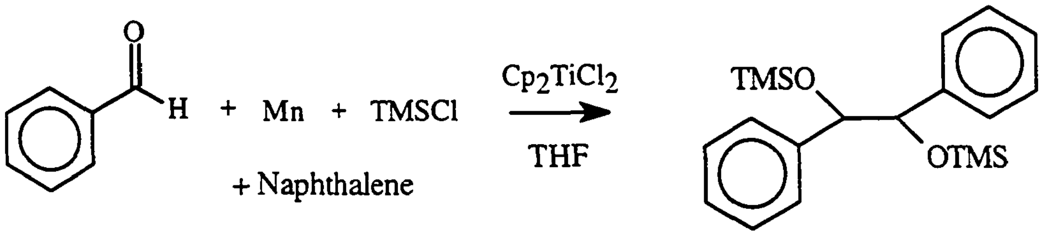
The pinacol experiments using both the bi- and trimetallic complex (6 and 7) in stoichiometric amounts were extremely informative. The results with the bimetallic complex 6 suggest that, when coordinated to the carbonyl substrates to form 5, it is responsible for the high diastereoselectivity. With the trimetallic complex 7, the low diastereoselectivity for the disilyl ether and the high diastereoselectivity for the acetal were also just as significant. The results with the trimetallic complex 7 suggest that a trimetallic complex coordinated to carbonyl substrates 8 is not responsible for the high *dl:meso* ratios seen in the catalytic system. This discovery contradicted the claims that a trimetallic intermediate **8** is responsible for the high diastereoselectivity in stoichiometric and catalytic pinacol coupling reactions promoted by $Cp_2TiCl_2/M$.

### *Kinetic Studies*

Kinetic studies were performed in an effort to determine the rate limiting step in the catalytic cycle. As described in chapter 3, pinacol couplings performed with aliphatic aldehydes are fairly slow. By knowing which step was rate determining, measures could potentially be taken to increase the speed of this step, thus making the overall catalytic reaction faster. Also of interest was the order of the reaction. If the order of the reaction was related to the titanium catalyst, some information about the active metallocene transition state intermediate (mono-, bi- or trimetallic) could be obtained.

The standard reaction for coupling benzaldehyde was performed using naphthalene as the internal standard. The amount of naphthalene used in a reaction was calculated to be identical to the amount of product after 10% conversion. With rare exceptions, reactions were monitored by the initial rate method in which only the first 10% of product formed is examined.[19] Once more than 10% product had been formed, the kinetic curve (product/time) was no longer linear and data could not be used to effectively calculate a rate constant.

**Scheme 5-15: Kinetic experiments using naphthalene as internal standard**



In each reaction, the concentration of one component was varied while the others were kept constant. Benzaldehyde, TMSCl and $Cp_2TiCl_2$ were all varied separately in pinacolization experiments. The titanium complex, manganese, and naphthalene were combined with THF and stirred until a green color was observed. Next, TMSCl was added followed by benzaldehyde. Aliquots were removed every few minutes.

The work-up described in chapter 2 was initially employed; however, in several reactions it appeared as if unreacted TMSCl in the aliquots removed was affecting the naphthalene to product ratio by desilylating some of the disilyl ether. Desilylation was not a problem in reactions that were run to completion because the majority of TMSCl had reacted and would not have influenced the product concentration. However, in the kinetic runs, all G.C.'s were taken within an hour of the addition of benzaldehyde. Hence, a significant amount of unreacted TMSCl was always present. This problem produced varying naphthalene:product ratios within a given sample that was injected on the G.C. at different times. A new work-up procedure was necessary to eliminate the unreacted TMSCl. The new procedure utilized a basic medium to quench the unreacted TMSCl. Samples were immediately quenched with aqueous $NaHCO_3$, extracted with ether, dried over $MgSO_4$, and filtered.

The initial results appeared promising when the a concentration of catalyst was varied. In Table 5-2, the correlation coefficients for the experiments varying the concentration of titanium complex were 90% and higher, and it was noted that when the concentration of catalyst was doubled, the rate of reaction doubled as well. However, upon examining other variables like TMSCl and benzaldehyde, it was discovered that no concentration/rate relationships could be determined. The results were nonlinear and irreproducible.

For TMSCl, no rate change was observed when the concentration of the silyl reagent was increased from 0.055 M to 0.11 M. When the concentration of TMSCl was doubled again (0.11 M to 0.22 M), a significant change in rate was observed. The trials using TMSCl as a variable did not assist in determining the order of the reaction. In fact, upon further experimentation, it was discovered that reproducibility could not be obtained for a given set of concentrations (see experiments using 0.22 M TMSCl).

**Table 5-2: Selected kinetic experiments[a]**

| Variable (mmol/ml) | Rate[b] (prod [c]/min) | $R^2$[c] |
|---|---|---|
| **$Cp_2TiCl_2$** | | |
| $2.5\times10^{-3}$ | $1.00\times10^{-2}$ | 0.97 |
| $0.5\times10^{-2}$ | $2.59\times10^{-2}$ | 0.93 |
| 0.01 | $4.82\times10^{-2}$ | 0.90 |
| **TMSCl** | | |
| 0.055 | $1.13\times10^{-2}$ | 0.96 |
| 0.11 | $1.00\times10^{-2}$ | 0.97 |
| 0.22 | $2.61\times10^{-2}$ | 0.93 |
| 0.22[d] | $5.32\times10^{-2}$ | 0.99 |
| **PhCHO** | | |
| 0.05 | $1.88\times10^{-2}$ | 0.96 |
| 0.10 | $1.00\times10^{-2}$ | 0.97 |
| 0.20 | $4.75\times10^{-2}$ | 0.95 |

[a] Constants were $Cp_2TiCl_2$ (2.5%), Mn (1.2 mmol), PhCHO (2.0 mmol), TMSCl (2.2 mmol), naphthalene (0.1 mmol), THF (20 ml). [b] Rate determined by amount of product relative to naphthalene in GC/time. [c] correlation coefficient, $R^2 = [xy]^2/[x^2][y^2]$ with x = product concentration and y = time (min). [d] Repeated run using 4.4 mmol TMSCl.

Variations of the benzaldehyde concentration within a kinetic run also did not yield conclusive results. As the concentration of the substrate was increased from 0.05 M to 0.10 M, a decrease in rate was observed. Next, when the concentration of benzaldehyde was further increased to 0.20 M, a dramatic increase in rate was observed. The trials varying benzaldehyde did not generate reproducible data to determine the order of the reaction. While the three trials could not be compared, the $R^2$ values within an individual run were over 95%, indicating a linear initial rate.

The experiments listed in Table 5-2 represent only a few of the kinetic runs performed to determine the kinetic reaction order of the pinacol reaction. Other concentrations of reagents were used in experiments, and a variety of work-up procedures were utilized until the optimal one described in the experimental section was adopted. Because of the inconsistent nature of the data, the order of the reaction with respect to the varied components could not be determined.

A few explanations may account for the failures with the kinetic experiments. First, the reactions were heterogeneous mixtures. Altering the rate of stirring even slightly could affect the rate of product formation. While altering the stirring may not be critical in a normal reaction that is allowed to run to completion, the kinetic experiments that focused on just the first 10% conversion may have been affected significantly by a change in stirring. Also, the temperature of the laboratory may have varied while the kinetic experiments were performed. The kinetic experiments were performed from early December until April. Temperatures changes (heat and air conditioner depending on weather outside) occurred in the laboratory during this time period. It is reasonable to suggest that a slight change in temperature may have affected the rate of pinacolization. Finally, the pinacolizations are air sensitive. While steps were taken to prevent air from entering the reaction vessel, it is conceivable that trace air may have entered the system. Trace air may not have affected the pinacol reactions run to completion. In the reactions monitoring only 10% product formation, the trace air could have a greater impact on the reaction and thus effect the data collected about the reaction rate.

Some adjustments to the procedure could be made to potentially eliminate the irreproducibility. First, only one model of stir plates could be employed with all kinetic runs. This step might reduce any inconsistencies in the rate of stirring. Also, the temperature could be more effectively controlled by using a temperature regulated water bath. Both of these adjustments are possible ways to solve the irreproducibility in the kinetic reactions. The problem of trace air entering the reaction vessel is not as easily addressed. Extreme air sensitive techniques were already followed in the pinacol coupling reactions. Both stirring and temperature variables can be regulated and thus improved in the kinetic runs. In contrast, further improvements in regards to the oxygen free atmosphere are not likely since air sensitive techniques were already in practice. Trace air entering the system remains a possible problem in the kinetic experiments.

## Conclusion

Studies were performed to probe the mechanism of the catalytic pinacol reaction. Through these experiments, some insight was gained to identify the pathway through which acetal was generated over the disilyl ether. Also, through the use of authentic samples of bi- and trimetallic complexes, 6 and 7, some understanding of the intermediates involved in coupling reaction was found. Kinetic studies were performed to determine the rate limiting step of the reaction as well as the order of the reaction.

The pathway through which acetal was generated was probed with several experiments. First, it was discovered that TMSCl played a crucial role in generating the acetal product even though it was not incorporated in the acetal structure. This result coincided nicely with the G.C. data (using an internal standard) that indicated disilyl ether was converted to acetal. Hence, TMSCl was necessary to form both disilyl and acetal.

Studies using synthesized samples of bi- and trimetallic complexes 6 and 7 were performed as well. These studies were very significant in that they contradicted the proposals published in the titanium-mediated pinacol area of research. The trimetallic/carbonyl intermediate 8 has been credited as the intermediate responsible for generating highly diastereoselective pinacol products. Our results indicated that it was not the trimetallic intermediate 8 but in fact the bimetallic intermediate 5 that was responsible for high *dl:meso* ratios in coupling reactions.

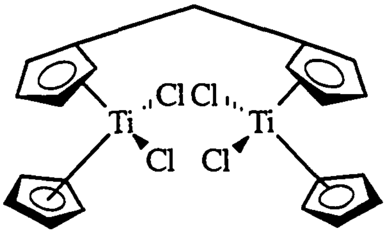
A series of kinetic reactions were performed to investigate what the order of the catalytic pinacol reaction was. Through these experiments, it was hoped to determine what the rate limiting step of the reaction was. Once the rate determining step was established, efforts could be made based on this knowledge to improve the yields and selectivities of the reactions. Also, it was thought that further evidence about the active transition state forming stereoselective pinacol product could be found in the order of the reaction. Unfortunately, the kinetic experiments produced very little consistent data that could be used to determine the rate limiting step. Extensive efforts were made to improve the reactions so that consistent data would be obtainable. As more improvements were made, it was discovered that reproducibility within a given run improved and yielded more linear data. However, outside of a particular kinetic run, data remained incongruous.

## Future Directions

Additional work exploring the mechanistic behavior of the catalytic pinacol reaction could be envisioned for the future. As discussed, significant information was discovered about possible metallic intermediates in the catalytic reaction through investigating both bi and trimetallic complexes. Metal complexes specifically designed to favor either a bi- or trimetallic intermediate like 5 and 8 could be constructed.

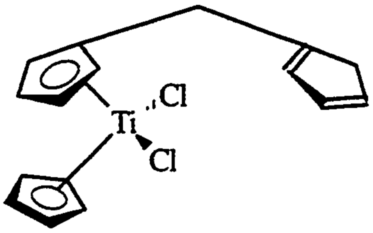
Extensive efforts were made to synthesize a known bimetallic titanium complex bridged with a methylene group:[20]

**Figure 5-3: Tethered metallocene**



Synthesis of this bridged titanium complex was achieved, but purification of the complex was not successful. Proton NMR and MS data indicated that a 1:1 mixture of the desired titanium complex and a mono-titanium complex (Figure 5-4) had formed.

**Figure 5-4: Tethered metallocene side-product**



While recrystalizations were ineffective in removing the monometallic compound, additional work can still be envisioned for generating the desired bimetallic tethered complex. The reaction between $2CpTiCl_3$ and $(CpCH_2Cp)Li_2$ to form the bimetallic complex could be slightly altered so that formation of a bimetallic complex would be favored over the monometallic one. A large excess of $CpTiCl_3$ in the reaction may favor formation of the bimetallic compound.

The tether in the complex (Figure 5-3) creates a unique conformational feature in this potential catalyst. The distance between the two titanium atoms was too small for another metal atom such as Mn to insert itself in the complex. Hence, a bimetallic intermediate could be enforced. By running pinacol reactions with this tethered metallocene, evidence for or against the suggested bimetallic intermediate could be discovered. If a bimetallic intermediate was truly operating in these pinacolizations, the tethered complex will further support that hypothesis by generating disilyl ether with high diastereoselectivity. However, if another intermediate (e.g. trimetallic) is responsible for generating pinacol product with high *dl:meso* ratios, the titanium complex would more than likely fail to yield the product stereoselectively.

Catalytic and stoichiometric experiments with this particular complex would have been interesting if the complex had been successfully purified. Although isolation of the methylene bridged complex was unsuccessful, additional complexes also designed to control the distance between the two titanium atoms could be investigated. Cyclohexyl, and ethylene tethers could be envisioned between the two cyclopentadienyl rings to produce a specific distance between titanium atoms. These type of catalyst variations would be a promising direction for the pinacol project.

## Experimental

### General

All starting materials were commercially obtained. Tetrahydrofuran was distilled under nitrogen from sodium and benzophenone. Glassware was oven dried (125°C) and flushed with nitrogen before use. Liquids were transferred using syringes, and all solids were manipulated within the dry box. Preparations for both the bi- and trimetallic intermediates were so air sensitive that all manipulations, including transferring solvents, were performed in the dry box.

$^1H$ and $^{13}C$ NMR spectra were obtained using a Varian XL-300 or a Varian Unity Inova-400 instrument. All NMR samples were dissolved in $CDCl_3$. A Hewlett Packard 5790A gas chromatograph and a Shimadzu GC-14A were used for monitoring reactions. GC/MS were obtained on a Hewlett Packard 5985 GC/MS instrument.

### Control Reaction without TMSCl

In a side-arm flask, $Cp_2NbCl_2$ (0.20 mmol, 60 mg ) and manganese (1.2 mmol, 66 mg) were combined under nitrogen. Dry THF (15 ml) was added to the vessel and the mixture was allowed to stir. After approximately 15 min, cyclohexanecarboxaldehyde (2.0 mmol, 0.20 ml) was added. The reaction was allowed to stir for 24 h at ambient temperature. Aliquots were removed and prepared through a series of filtrations with Celite and triturations using petroleum ether and ether (procedure described in chapter 2). Aliquots were injected on the G.C. and showed no indication of pinacolization.

### Synthesis of bi and trimetallic complex (6 and 7)

### Bimetallic complex, $[Cp_2TiCl]_2$, 6[12]

Aluminum foil ( 24.1 mmol, 0.650g), activated with $HgNO_3$, was weighed into a round bottom flask inside of the dry box. Also, titanocene dichloride (4.03 mmol, 1.00 g) and dry THF (100 ml) were added to the reaction flask containing the activated aluminum. The mixture was stirred for 24 h and was dark green after this time period. The mixture was filtered within the dry box. The collected filtrate was concentrated using a vacuum line and then triturated using ether (to remove $AlCl_3$). Some product was lost during this step because of its slight solubility in ether. A dark gray/brown solid with a tint of green remained after the trituration step. It was further dried using the vacuum line. No yield or spectra data was determined due to the extreme reactivity of complex 6. Coutts indicated that the bimetallic intermediate appeared greenish-brown; this color was seen in the material isolated from our reaction.

### Trimetallic complex, $[Cp_2TiCl]_2MnCl_2$, 7[13,14]

Titanocene dichloride (4.0 mmol, 1.0 g), manganese (2.0 mmol, 110 mg) and dry THF (20 ml) were combined in a round bottom flask inside of the dry box. The mixture was stirred at ambient temperature for 24 h, turning from red to green after several hours. The mixture was filtered inside of the dry box affording a green solid which was further dried on the vacuum line. No yield or spectral data was determined due to the extreme reactivity of complex 7. Other trimetallic complexes (Ti-M-Ti where M= Zn or Mg) isolated by Stucky and Stephan appeared as green crystals. The trimetallic intermediate which was isolated was also green.

### Study of acetal formation with internal standard *via* pinacolization

All manipulations for this reaction were performed in the dry box due to the sensitive nature of the trimetallic reagent employed. To a side arm flask, the trimetallic complex 7 (0.302 mmol, 0.275 g) and naphthalene (0.60 mmol, 77 mg) were added. Dry THF (15 ml) was added to the flask and the mixture was allowed to stir for 15 min. Next, TMSCl (0.50 mmol, 0.10 ml) and benzaldehyde (0.60 mmol, 0.10 ml) were added by syringe. The mixture remained in the dry box and stirred at ambient temperature. Aliquots were removed from the box and processed through a series of filtrations and triturations (see standard procedure, chapter 2). The aliquots were then injected on the G.C. and analyzed.

### Pinacolization using stoichiometric amounts of 6 and 7

#### Bimetallic complex, 6

All reagents were combined in the dry box and the reaction was performed within the dry box; aliquots were removed from the box to be analyzed on the G.C. The $[Cp_2TiCl]_2$ 6 (0.500 mmol, 210 mg) and THF (15 ml) were combined in a side arm flask and allowed to stir. The silyl reagent, TMSCl (1.1 mmol, 0.14 ml), was added followed by benzaldehyde (1.0 mmol, 0.10 ml). The reaction contents were allowed to stir at room temperature for several days. Aliquots were removed from the reaction and worked-up outside of the dry box. Each aliquot was filtered through Celite and concentrated. The remaining residue was triturated with petroleum ether: ether (4:1) and filtered through Celite again. This filtrate was injected onto the G.C. and analyzed.

#### Trimetallic complex, 7

The procedure used in the pinacol reaction with the bimetallic complex 6 was applied here as well. This reaction was run for 24 h. The amount of each reagent was slightly different: The trimetallic complex 7 (0.302 mmol, 0.275 g), benzaldehyde (0.60 mmol, 0.10 ml), TMSCl (0.50 mol, 0.10 ml),and THF (15 ml) were used in this experiment. Results were determined by G.C. analysis

### Kinetic studies using internal standard during pinacolization

To a side arm round bottom flask was added titanocene dichloride (0.05 mmol, 14 mg), manganese (50 mesh, 1.2 mmol, 66 mg), and naphthalene (0.10 mmol, 13 mg) under nitrogen. Distilled THF (20 ml) was added and the mixture was stirred for 15 min while changing from red to green. Chlorotrimethylsilane (2.2 mmol, 0.28 ml) was added *via* syringe followed by the aldehyde (2.0 mmol, 0.20 ml). Aliquots (approx. 0.5 ml) were removed while the reaction was in progress. The aliquots were immediately quenched with aqueous $NaHCO_3$ followed by extraction with ether. The ether extracts were dried over $MgSO_4$ and filtered through Celite. The isolated material was injected on the G.C. and the ratio of product to naphthalene was determined. All G.C. aliquots were removed within one hour of the reaction to observe only the first 10% of product formation. The concentrations for three reagents were altered in different reactions while the remaining concentrations were held constant. The concentrations of benzaldehyde, TMSCl, and $Cp_2TiCl_2$ were all varied in kinetic experiments. Only one variable was altered per experiment. For instance, when a benzaldehyde concentration of 1.0, 2.0, or 4.0 mmol was used, the other reagents in the reactions remained the same.

1. benzaldehyde: 0.05 M, 0.10 M, 0.20 M; all other variables remained constant
2. TMSCl: 0.055 M, 0.11 M, 0.22 M; all other variables remained constant
3. $Cp_2TiCl_2$: $2.5x10^{-3}$ M, $0.50x\ 10^{-2}$ M, 0.01 M; all other variables remained constant

## Characterization of acetals:

Acetals were isolated using the same pinacol work-up procedure (filtrations and triturations) employed for isolating disilyl ethers. Acetals were characterized by $^1$H NMR and GC/MS.

*2,4,5-tricyclohexyl-1,3-dioxolane*

*$^1$H NMR ($CDCl_3$) $\delta$ dl* isomer: 0.8-1.9 (m, 33H), 3.18 (dd, J= 6 Hz, 8.7 Hz, 1H), 3.34 (dd, J= 6 Hz, 9 Hz, 1H), 4.08 (d, J= 7.5 Hz, 1H); *meso* 1: 0.8-1.9 (m, 33H), 3.58 (d, J= 5.4 Hz, 2H), 4.41 (d, J= 7.2 Hz, 1H); *meso* 2: 0.8-1.9 (m, 33H), 3.64 (d, J= 5.7 Hz, 2H), 4.61 (d, J= 4.8 Hz, 1H); *GC/MS 12ev EI* m/e (intensity): 319 ($M^+$-1, 1.6), 237 ($M^+$-83, 85.2), 208 ($M^+$- 112, 17.4), 192 ($M^+$-128, 117), 109 ($M^+$-211, 95.0)

*2,4,5-triphenyl-1,3-dioxolane*

*$^1$H NMR ($CDCl_3$) $\delta$ dl* isomer: 4.95 (d, J= 8.1 Hz, 1H), 4.98 (d, J= 7.8 Hz, 1H), 6.41 (s, 1H), 7.25-7.80 (m, 15H); *meso*: 5.54 (s, 2H), 6.21 (s, 1H), 7.25-7.80 (m, 15H); *GC/MS 12ev EI* m/e (intensity): 196 ($M^+$-106, 100), 180 ($M^+$-122, 2.3), 103 ($M^+$-199, 0.2)

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