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## Asymmetric Catalysis in Organic Synthesis

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Damon R. Click, Steven K. Grumbine,  
Brian L. Scott, and John G. Watkin\* (CST-18)

### Abstract

This is the final report of a three-year, Laboratory Directed Research and Development (LDRD) project at the Los Alamos National Laboratory (LANL). The goal of the project was to prepare new catalyst systems, which would perform chemical reactions in an enantioselective manner so as to produce only one of the possible optical isomers of the product molecule. We have investigated the use of lanthanide metals bearing both diolate and Schiff-base ligands as catalysts for the enantioselective reduction of prochiral ketones to secondary alcohols. The ligands were prepared from cheap, readily available starting materials, and their synthesis was performed in a "modular" manner such that tailoring of specific groups within the ligand could be carried out without repeating the entire synthetic procedure. In addition, we have developed a new ligand system for Group IV and lanthanide-based olefin polymerization catalysts. The ligand system is easily prepared from readily available starting materials and offers the opportunity to rapidly prepare a wide range of closely related ligands that differ only in their substitution patterns at an aromatic ring. When attached to a metal center, the ligand system has the potential to carry out polymerization reactions in a stereocontrolled manner.

### Background and Research Objectives

The modern pharmaceuticals and fine chemical industries are heavily reliant upon the ability to produce biologically active organic compounds (antibiotics, flavorings, pesticides, anesthetics, sweeteners *etc.*) of high optical (enantiomeric) purity.<sup>1</sup> At one time, many drugs were supplied as racemic mixtures (containing equal quantities of both enantiomers) with the assumption that one enantiomer would perform the desired therapeutic function while the other would be harmlessly excreted. However, the catastrophic effects of the drug Thalidomide, sold in the 1960s as a racemic mixture, were traced to the supposedly benign (S)-isomer of the drug and since then the enantiomeric purity of many pharmaceutical products has been controlled by federal regulations.

The preparation of a single enantiomer of a chiral organic molecule can generally be accomplished in one of two ways: (a) preparation of a racemic mixture followed by mechanical or chemical separation of the two enantiomers or (b) enantioselective synthesis in which only the target isomer is produced. The majority of pharmaceuticals are currently produced using the first of these methods, with the enantiomers often being separated by

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tedious fractional crystallizations. The major drawback of this approach is that the unwanted enantiomer is almost always of no commercial value and thus one half of the painstakingly prepared compound can end up in the waste stream. Thus the development of new asymmetric catalysts, which are capable of transforming prochiral starting materials into optically pure products, is an area of rapidly expanding research interest.

A number of classes of asymmetric catalysts are now fairly well established, including asymmetric hydrogenation catalysts, which generally contain chiral phosphine ligands attached to a late transition metal center, and asymmetric epoxidation catalysts, which have utilized titanium and manganese as the active metal centers. Due to our extensive experience in the field of f-element chemistry, our interest lay in the development of new asymmetric catalysts based around a lanthanide metal center. A number of literature reports had indicated that bis-cyclopentadienyl lanthanide-based catalysts exhibited particularly high activities for reactions such as hydrogenation and hydrosilylation.<sup>2</sup> Thus we set out to investigate the catalytic activity and enantioselectivity of chiral lanthanide-based catalysts that contained alkoxide and/or Schiff-base ligands, and to develop a program in catalytic enantioselective synthesis of organic molecules based upon an approach that combined rational ligand design, structure elucidation and molecular modeling.

#### **Importance to LANL's Science and Technology Base and National R&D Needs**

The implementation of a program in catalytic asymmetric synthesis at Los Alamos was expected to reap benefits with respect to the potential for collaboration with industrial sponsors, and also enhance the Laboratory's reputation in the field of catalysis. On a national scale, the need for new asymmetric technologies to supply the pharmaceutical and fine chemical industries is growing rapidly, since sales of single enantiomers of chiral drugs are expected to grow at the expense of racemic mixtures (see table below). For example, the anti-inflammatory drug Naproxen (sales of \$1 billion per annum) is currently produced as a racemic mixture and the enantiomers separated by repeated fractional crystallization, but the procedure is shortly to be replaced by an enantioselective hydrogenation process that will produce only the desired (S)-isomer.

#### **Sales of 25 top-selling prescription drugs, \$ billions**

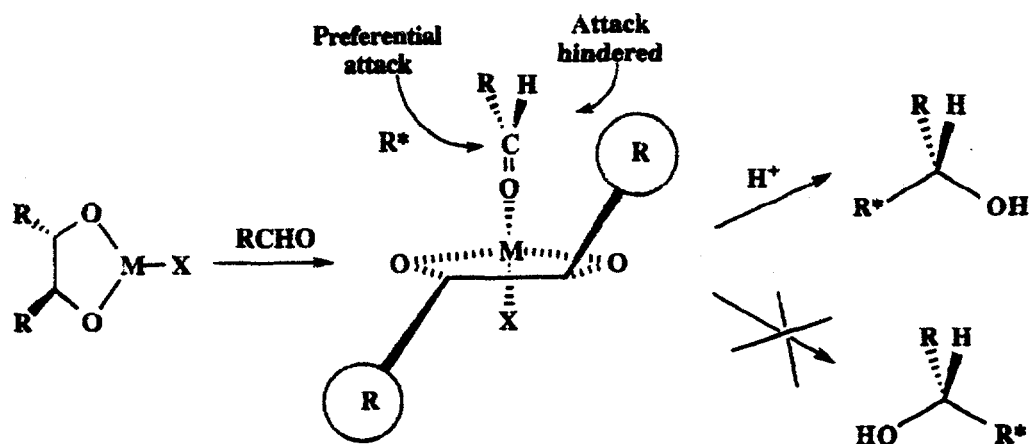
<b>Drug Category</b>	<b>1993</b>	<b>1994</b>	<b>1995</b>	<b>1996</b>	<b>% annual change</b>
Achiral	8.4	9.5	9.8	10.2	+7.0
Racemic	3.9	3.0	2.2	1.4	-29.5
Enantiomeric	22.1	23.0	24.8	26.7	+6.6
<b>TOTAL</b>	<b>34.4</b>	<b>35.5</b>	<b>36.8</b>	<b>38.3</b>	<b>+3.7</b>
ENANTIOMERIC	64.3 %	64.8 %	67.4 %	69.7 %	

## Scientific Approach and Accomplishments

Our major objective in this research program was to develop novel catalytic species, based around the framework of a lanthanide metal center, which would catalyze organic transformations in a highly efficient and highly enantiospecific manner. In addition, we aimed to minimize the quantity of catalyst required to achieve highly enantioselective bond-forming reactions by producing catalysts of high activity. Catalytic asymmetric synthesis is highly attractive from a financial standpoint since it allows the production of large quantities of optically pure compounds from optically inactive precursors, through the use of small quantities of chiral catalyst. This benefit is outweighed, however, if the catalyst is extremely expensive compared to the value of the product. Thus a second important goal was to design catalytic species employing chiral ligands that can be readily synthesized from cheap, naturally occurring starting materials.

Our rational approach to enantioselective catalysis focused upon two main areas: (1) tailoring the Lewis acidity of the metal center and (2) a flexible, "modular" approach to chiral ligand design.

(1) An enantioselective catalyst must firstly allow the binding of a prochiral substrate molecule in a manner that produces an asymmetric environment about the substrate (*e.g.* an aldehyde bound to the chiral diolate complex shown in Figure 1). Approach of a reactant molecule ( $R^*$ ) to the catalyst/substrate complex is dictated by the environment about the substrate, which in this example forces the reactant to preferentially approach from the left side of the substrate and consequently to favor the formation of only one isomer of the alcohol product. Thus it is extremely important that the metal center



**Figure 1.** Idealized view of the influence of a chiral ligand on addition of a nucleophile to an aldehyde.

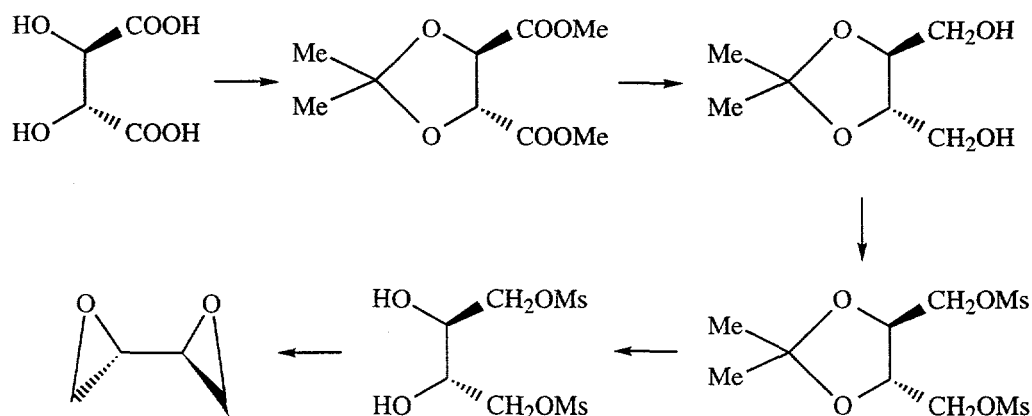
should be capable of tightly binding the substrate molecule within this asymmetric environment until reaction is complete, and equally that the chiral ligand must remain bound to the metal center throughout the catalytic cycle.

The presence of a Lewis acidic metal center is crucial in ensuring adequate binding of the substrate, while use of a chelating ligand such as the diolate shown in Figure 1 ensures that the second requirement is met. Lanthanide alkoxide complexes are known to exhibit pronounced Lewis acidic character, and it has been reported that the relative catalytic activity of metal alkoxide complexes in a nitroaldol reaction was  $\text{La(OR)}_3 > \text{Zr(OR)}_4 > \text{Ti(OR)}_4$ , which is in agreement with the ranking of Lewis acidity of the metal centers.<sup>3</sup> To further increase the Lewis acidity of the metal center we planned to introduce fluorinated alkoxide ligands ( $\text{R}_f\text{O}^-$ ), in which highly electronegative fluorine substituents substantially reduce the electron density donated by the oxygen lone pairs to the metal center.

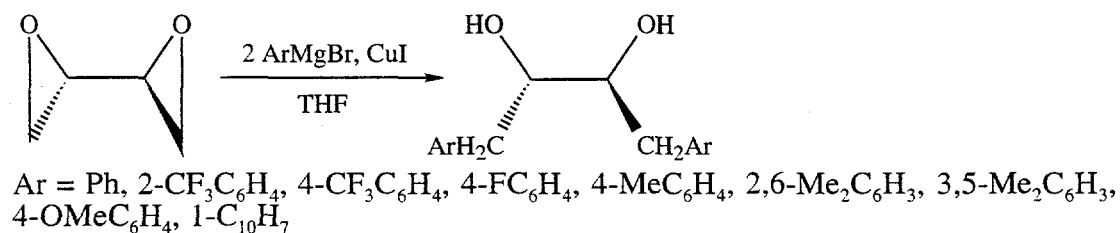
(2) The ability to prepare a wide range of chiral ligands, and the possibility of performing subtle changes in their design (*e.g.* addition of extra blocking methyl groups), was crucial to the success of this project. We elected to concentrate initially upon alkoxide ligands for three main reasons: they are resistant to many reaction conditions under which ligands such as alkyl, amide or thiolate would be protonated and lost from the coordination sphere of the metal; we have extensive experience in the synthesis, characterization and reactivity of f-element alkoxide complexes;<sup>4</sup> and chiral alcohols and diols are readily synthesized from cheap, commercially available starting materials. For example, optically pure 1,2-diols are available *via* treatment of chiral butadiene diepoxide, which is itself produced from cheap L-tartaric acid with a Grignard reagent.<sup>5</sup> The great advantage of this 'modular' approach is that subtle changes in the design of the diol ligand are accomplished simply by modification of the Grignard reagent rather than having to repeat the entire ligand synthesis.

The use of sterically demanding chiral ligands was expected to produce catalyst species of low nuclearity, which itself is of significant benefit. For example, lanthanide-based catalysts employing the commercially available binaphthol ligand have been reported to undergo 'aging' effects, and consequently have to be used as soon as they are prepared. Placement of sterically demanding aryl groups on the backbone of the diol ligands was expected to prevent oligomerization and 'aging' effects in the catalyst systems.

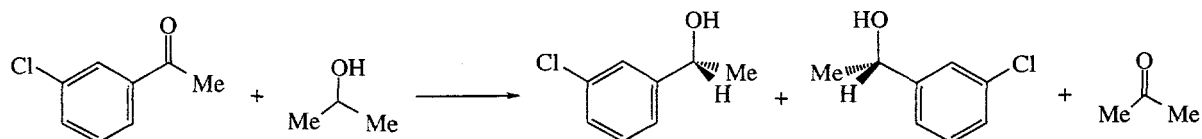
Thus our synthetic approach began by optimizing the preparation of the optically pure starting material (S,S)-butadiene diepoxide, which was available in 5 steps from tartaric acid as shown below. We successfully scaled up this synthesis such that the diepoxide could be prepared in batches of 50 g. We had specifically chosen the butadiene



diepoxide as starting material since subsequent reaction of the diepoxide with two equivalents of aryl Grignard reagent in the presence of copper(I) iodide led to the isolation of a range of chiral diols  $\text{ArCH}_2\text{CH}(\text{OH})\text{CH}(\text{OH})\text{CH}_2\text{Ar}$  bearing substituted aromatic rings as shown below. Thus we were able to rapidly prepare a wide range of chiral diol ligands bearing substituents such as methoxy, methyl and fluoro without having to repeat a multiple step synthesis for each example. All of the diol ligands were isolated as crystalline solids that were characterized by  $^1\text{H}$  NMR, IR and microanalysis.

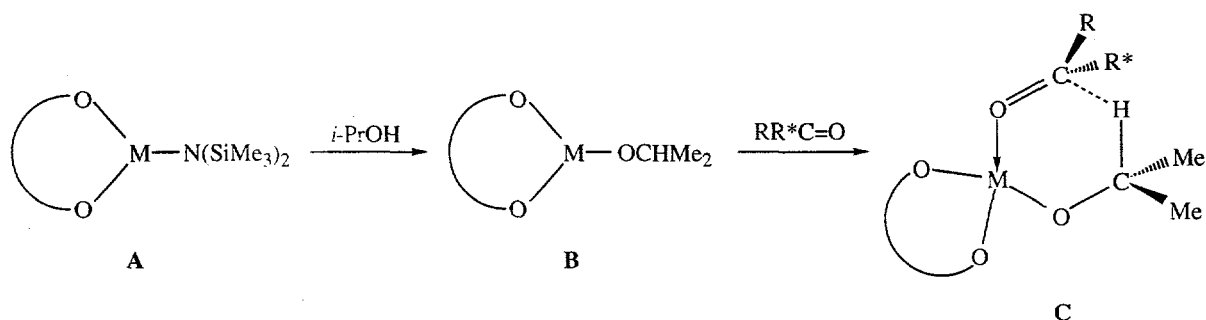


One equivalent of the diol ligand was allowed to react with the lanthanide tris(amide) precursor complex  $\text{Ln}[\text{N}(\text{SiMe}_3)_2]_3$  ( $\text{Ln} = \text{Sm}, \text{Gd}, \text{Nd}, \text{Dy}, \text{Er}, \text{Yb}$ ) and the resulting solutions or suspensions were used in the Meerwein-Ponndorf-Verley (MPV) reduction of 3-chloroacetophenone:



Conditions: 5 mol % catalyst, 2 ml THF, 0.5 ml *i*-PrOH, room temperature, 24 h

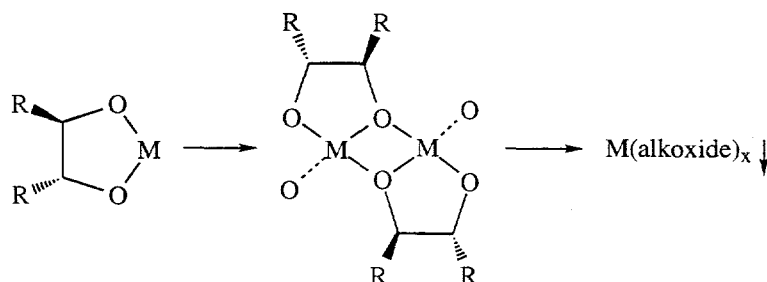
In this reaction, the initial lanthanide diolate amide species (**A**) reacts with *iso*-propanol to form an *iso*-propoxide derivative (**B**). Binding of the prochiral ketone to the metal center then allows the establishment of the six-membered transition state shown below (**C**) in which a hydride ligand is transferred from *iso*-propoxide to the coordinated ketone. The chiral nature of the diolate ligand will exert an influence upon the orientation of the bound ketone, such that the hydride ligand is preferentially transferred to one face of the ketone over the other. Hydrolysis of the reaction mixture subsequently liberates the secondary alcohol product.



While the yields of the reaction were generally good (see table below), the rate was found to be rather slow, and several hours were required for the reaction to proceed to completion. The optical purity of the resulting secondary alcohol product was generally low, with the best result being obtained when the 3,5-dimethylphenyl substituted diol was used in combination with the gadolinium tris(amide) precursor - in this case a 78% yield of secondary alcohol was obtained that had optical purity (or enantiomeric excess, ee) of 14%.

Entry	Catalyst Precursor	Diol ligand	Yield (%)	ee (%)
1	$\text{Dy}[\text{N}(\text{SiMe}_3)_2]_3$	$\text{Ar} = 4\text{-CF}_3\text{C}_6\text{H}_4$	90	9
2	$\text{Gd}[\text{N}(\text{SiMe}_3)_2]_3$	$\text{Ar} = 2\text{-CF}_3\text{C}_6\text{H}_4$	85	1
3	$\text{Nd}[\text{N}(\text{SiMe}_3)_2]_3$	$\text{Ar} = 4\text{-MeOC}_6\text{H}_4$	90	1
4	$\text{Gd}[\text{N}(\text{SiMe}_3)_2]_3$	$\text{Ar} = 3,5\text{-Me}_2\text{C}_6\text{H}_3$	78	14
5	$\text{Gd}[\text{N}(\text{SiMe}_3)_2]_3$	$\text{Ar} = \text{H}$	36	17

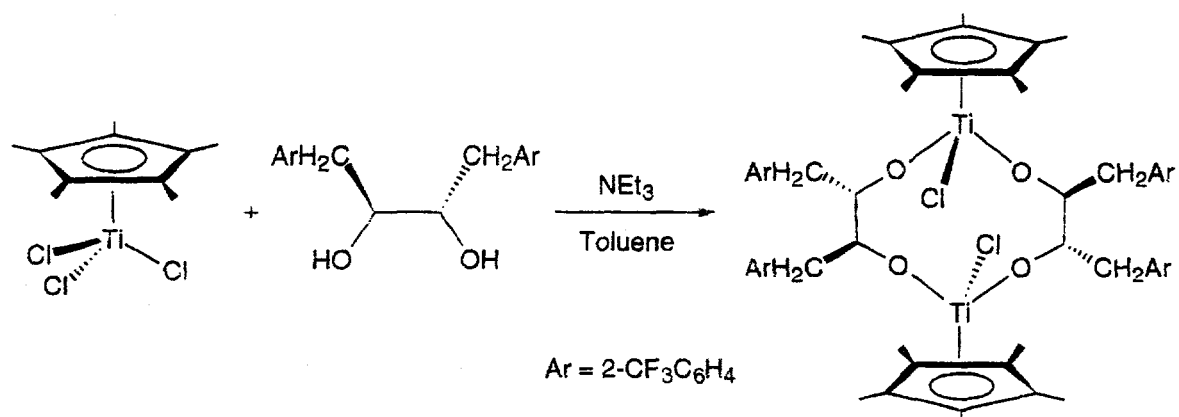
It was noted that the reaction of lanthanide tris(amide) solutions with the chiral 1,2-diols was sometimes found to produce rather insoluble materials. The formation of alkoxides of low solubility is often an indication of oligomerization taking place by means of oxygen bridging:



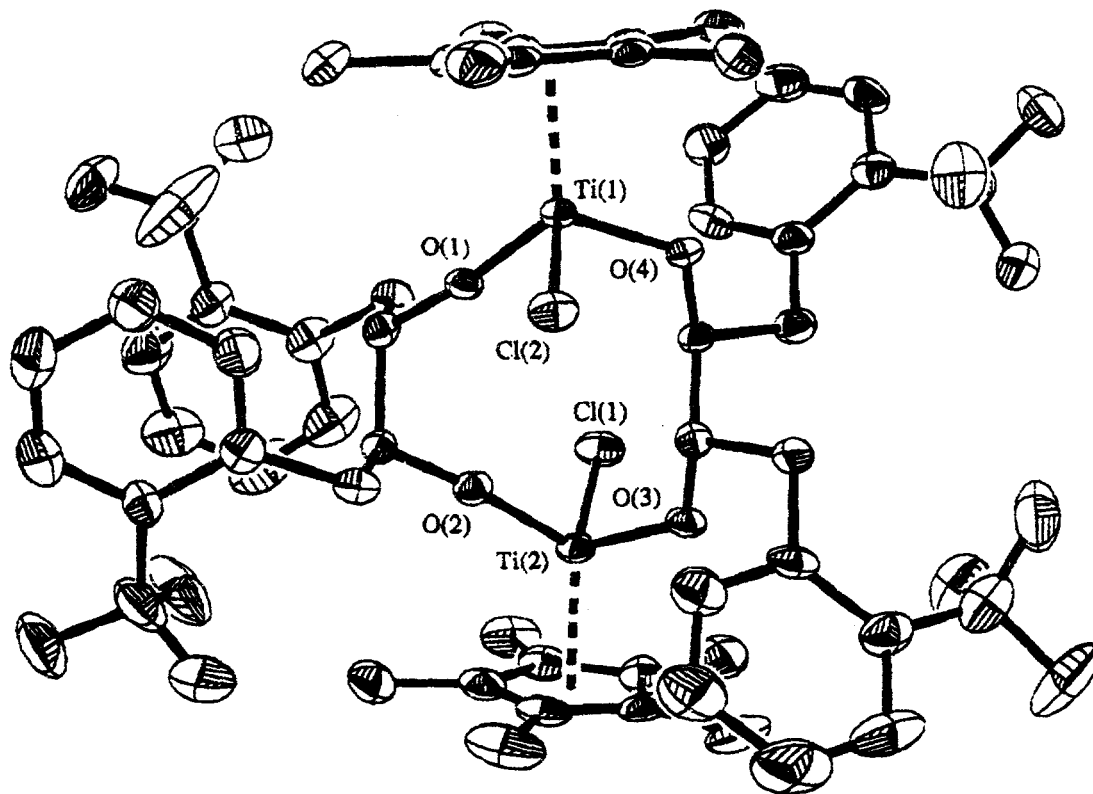
The formation of such oligomers may lead to the presence in the reaction mixture of more than one type of coordination geometry for the lanthanide metal center, and thus multiple potential catalytic sites rather than the ideal "single site" structure that is most desirable for an enantioselective catalyst. This may account in part for the low enantioselectivity of the lanthanide diolate complexes in the MPV reduction.

It was also notable that when the bulky aryl groups were replaced by hydrogen atoms (entry 5), the enantioselectivity was not adversely affected. This led to speculation that the methylene group between the two-carbon backbone and the aryl group was allowing free rotation of the aryl group and thus nullifying its effectiveness as a directing group. Thus it appeared that the 1,2-diolate ligands suffered two major drawbacks: their steric requirement was insufficient to prevent oligomerization of the catalyst, and the presence of the methylene groups led to lack of rigidity in the ligands and thus a loss of directing influence.

In order to gain insight into the mode of binding of the diolate ligands to a metal center, attempts were made to prepare single crystals of both lanthanide and Group IV derivatives of the diolate ligands. Thus pentamethylcyclopentadienyltitanium trichloride was found to react with one equivalent of the *ortho*-trifluoromethyl substituted diol (2*S*,3*S*)-2-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CHOHCHOHCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-2-CF<sub>3</sub> in toluene in the presence of triethylamine to produce the diolate complex [( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)TiCl( $\mu$ -diolate)]<sub>2</sub> as shown below.



In the solid state, the overall molecular geometry consists of two titanium metal centers, each bearing a pentamethylcyclopentadienyl ligand and a terminal chloride ligand, bridged by two diolate ligands such that a central 10-membered ring is formed (Figure 2).

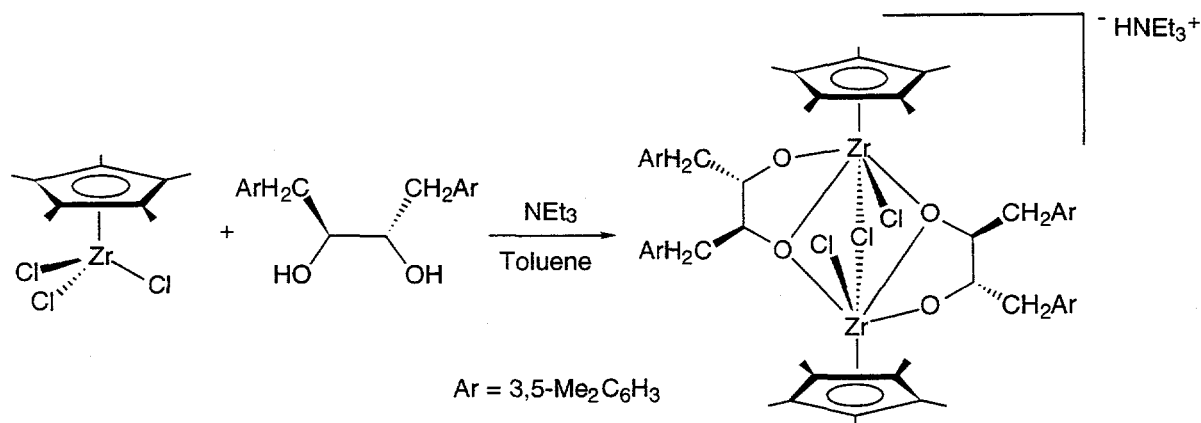


**Figure 2.** ORTEP plot (50% probability ellipsoids) showing the molecular structure of  $[(\eta\text{-C}_5\text{Me}_5)\text{TiCl}(\mu\text{-diolate})]_2$ .

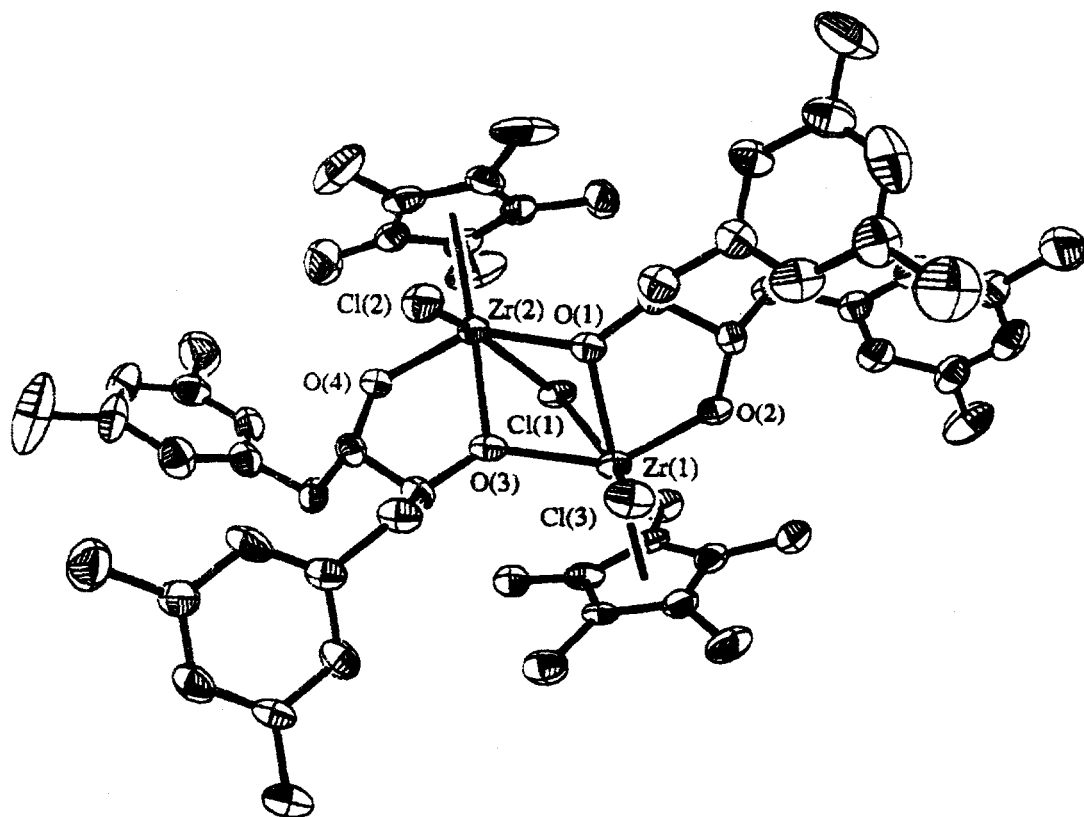
Similar coordination geometries have been observed previously in the chemistry of the Group IV metals, notably the titanium pinacolato species  $[(\eta\text{-C}_5\text{H}_5)\text{TiCl}(\mu\text{-OCMe}_2\text{CMe}_2\text{O})]_2$ <sup>6</sup> and the zirconium dimethyl tartrate complex  $[(\eta\text{-C}_5\text{H}_5)_2\text{Zr}(\mu\text{-MeO}_2\text{COCH}_2\text{CH}_2\text{OCO}_2\text{Me})]_2$ .<sup>7</sup>

The geometry about the metal center resembles a three-legged piano stool, with  $\text{Cp}_{\text{centroid}}\text{-M-Cl}$  and  $\text{Cp}_{\text{centroid}}\text{-M-O}$  angles ranging from  $111.3(3)^\circ$  to  $123.3(3)^\circ$ . Terminal Ti-Cl bond lengths are both  $2.306(2)$  Å, while Ti-O distances ranging from  $1.783(4)$  to  $1.830(5)$  Å are typical of those previously observed for terminal titanium alkoxide ligands.<sup>8</sup> One of the most notable features of the solid-state structure is the widely differing conformations adopted by the two bridging diolate ligands. Thus one of the diolate ligands possesses very large Ti-O-C angles of  $172.3(4)$  and  $172.4(4)^\circ$ , while the other displays rather acute Ti-O-C angles of  $125.2(4)^\circ$ . Minor differences in Ti-O bond lengths are observed between the diolate ligand with large Ti-O-C angles (Ti-O =  $1.791(5)$  and  $1.783(4)$  Å) as compared to the ligand with acute Ti-O-C angles (Ti-O =  $1.830(5)$  and  $1.828(4)$  Å). The pairs of distances are in agreement with the generally accepted view that a more obtuse M-O-C angle equates to greater  $\text{O}\rightarrow\text{M}$   $\pi$ -donation and a shorter M-O bond length. Despite the widely differing conformations of the diolate ligands, the central  $\text{Ti}_2\text{O}_4\text{C}_4$  core resembles a cyclohexane ring in a chair conformation, as was observed in the pinacolato complex  $[(\eta\text{-C}_5\text{H}_5)\text{TiCl}(\mu\text{-OCMe}_2\text{CMe}_2\text{O})]_2$ .<sup>6</sup>

A directly analogous reaction employing the 3,5-dimethylphenyl substituted diol ligand and pentamethylcyclopentadienylzirconium trichloride led to isolation of the salt complex  $[\text{HNEt}_3][(\eta\text{-C}_5\text{Me}_5)_2\text{Zr}_2\text{Cl}_2(\mu\text{-Cl})(\mu\text{-diolate})_2]$ , in which an equivalent of triethylammonium chloride had been retained by the dimeric zirconium diolate species:



The overall molecular geometry of the zirconium-containing anion comprises two ( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)ZrCl moieties bridged by a single bridging chloride ligand and two diolate ligands. One oxygen atom within each diolate ligand acts as a bridge between the zirconium metal centers while the other is bound in a terminal fashion to one metal center. The structure thus contains one Zr<sub>2</sub>O<sub>2</sub> four-membered ring and two ZrO<sub>2</sub>C<sub>2</sub> five-membered rings (Figure 3).



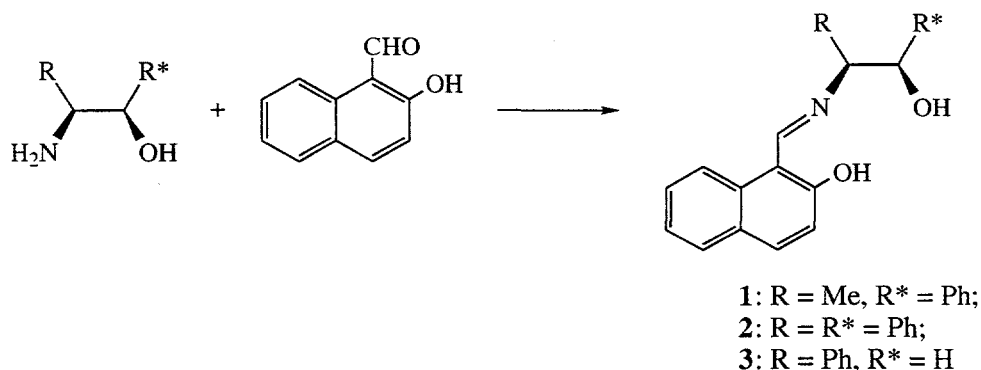
**Figure 3.** ORTEP representation (50% probability ellipsoids) of the anion of the salt complex [HNEt<sub>3</sub>][( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)<sub>2</sub>Zr<sub>2</sub>Cl<sub>2</sub>( $\mu$ -Cl)( $\mu$ -diolate)<sub>2</sub>].

The geometry about the zirconium metal centers may best be described as a distorted octahedral with the bridging oxygen atoms occupying positions effectively *trans* to the pentamethylcyclopentadienyl ligands. The M-O and M-Cl bonds *cis* to the pentamethylcyclopentadienyl ligand tend to distort away from it, and define angles ranging from 99.9(5) to 116.8(5)° with the C<sub>p</sub>centroid-M vector. The bridging chloride ligand adopts a somewhat asymmetric position, having a Zr-Cl distance of 2.606(4) Å to Zr(1)

and 2.737(3) Å to Zr(2). The asymmetry cannot be ascribed to a *trans* effect since both bridging Zr-Cl bonds lie effectively *trans* to a terminal chloride ligand. Both of the bridging Zr-Cl distances are, however, comparable to those found in other structurally characterized complexes containing Zr-Cl-Zr linkages.<sup>9</sup> Terminal Zr-Cl bond lengths are also substantially different from one another (2.499(4) and 2.584(4) Å), with the shorter Zr-Cl distance being associated with the zirconium possessing the longer Zr-Cl bridging distance. Terminal Zr-O distances of 1.989(9) and 1.972(9) Å are very similar to those observed in the zirconium tartrate complexes described by Erker *et al.*,<sup>7</sup> and the 1,2-cyclohexanediolate species [ZrCl<sub>3</sub>(THF)<sub>2</sub>]<sub>2</sub>(μ-1,2-O<sub>2</sub>C<sub>6</sub>H<sub>10</sub>).<sup>10</sup> Bridging Zr-O distances are, as expected, longer than terminal Zr-O bond lengths, and range from 2.125(9) to 2.222(8) Å. The central four-membered Zr<sub>2</sub>O<sub>2</sub> ring deviates somewhat from planarity, with the internal angles summing to 342.7°.

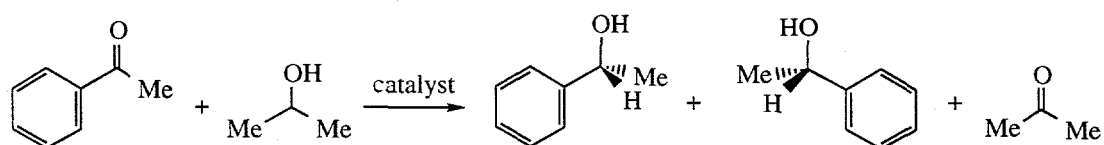
The observation of dimeric structures in both of these cases lends weight to the argument that the diolate ligands are insufficiently bulky to produce monomeric catalytic species, especially with the lanthanide metals which are significantly larger than a titanium or zirconium metal center. Therefore we began to design chiral ligands that would provide a more sterically demanding and more rigid directing environment about the metal center, while maintaining our goal of using simple, cheap starting materials.

We found that the reaction of 2-hydroxynaphthaldehyde with a range of commercially available amino-alcohols led to the isolation of highly crystalline Schiff-base compounds, which reacted with lanthanide tris(amide) complexes to produce catalytically active species:



Molecular modeling studies suggested that these Schiff base ligands would be capable of chelating the metal center more effectively than the simple diolate ligands, and that their steric bulk and 3-point attachment to the metal center would help to prevent

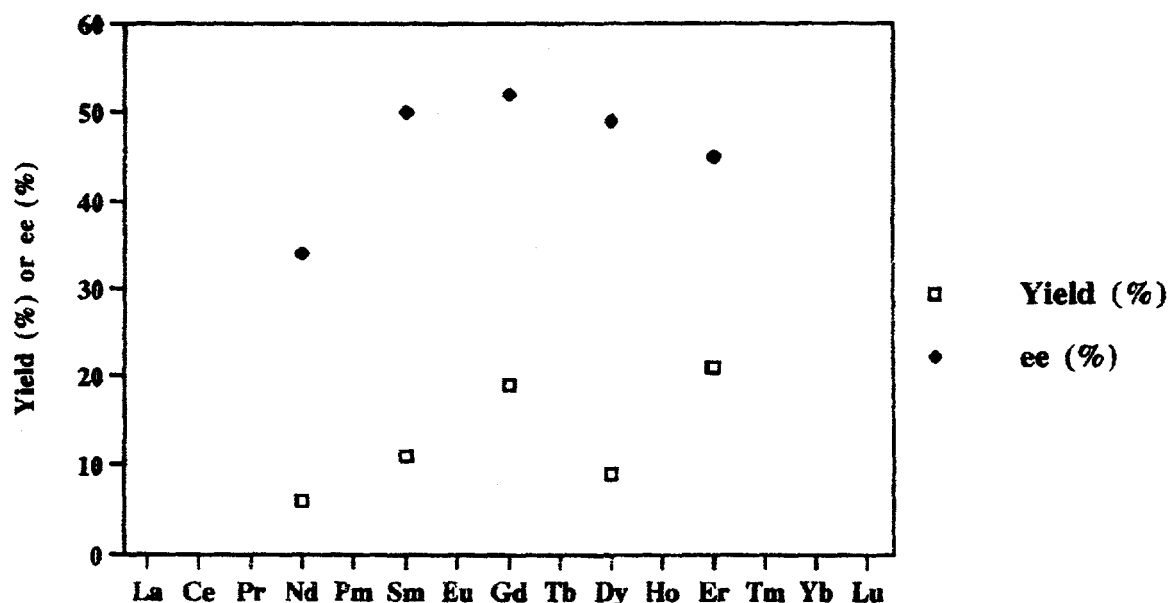
oligomerization. They would also provide an asymmetric environment about the metal center, which was significantly more rigid than that provided by the 1,2-diol ligands employed above. The Schiff base ligands **1-3** above were allowed to react with lanthanide tris(amide) precursors and the resulting solutions used in the MPV reduction of acetophenone:



Conditions: 5 mol % catalyst, 2 ml THF, 0.25 ml *i*-PrOH, 24 h

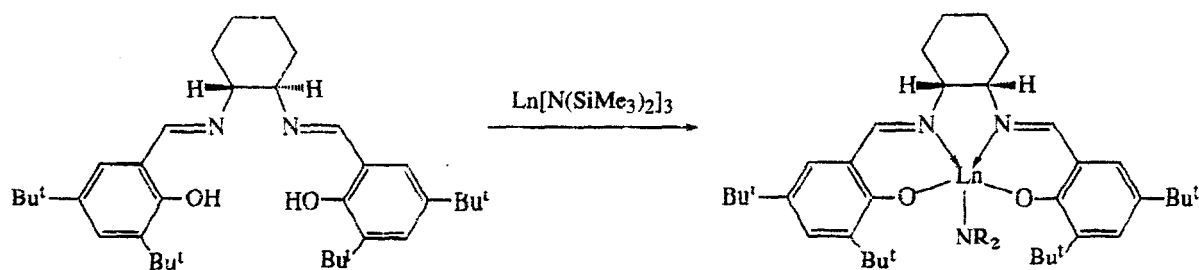
Catalyst Precursor	Ligand	Temp. (°C)	Yield (%)	ee (%)
Dy[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	20	9	49
Gd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	20	19	52
Er[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	20	21	45
Sm[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	55	10	38
Nd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	55	13	43
Sm[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	20	11	50
Nd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>1</b>	20	6	34
Nd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>2</b>	20	29	20
Sm[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>2</b>	20	18	9
Sm[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>3</b>	20	56	27
Nd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>3</b>	20	46	12
Sm[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>2</b>	55	22	0
Nd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>2</b>	55	22	7
Nd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>3</b>	55	60	16
Sm[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>3</b>	55	51	24

We were able to plot the variation in reaction yields and enantioselectivities as the metal center alone was varied, with all other variables remaining constant (Figure 4). Ideally, both the yield and enantioselectivity of the reaction would be optimized for the same metal within the lanthanide series.

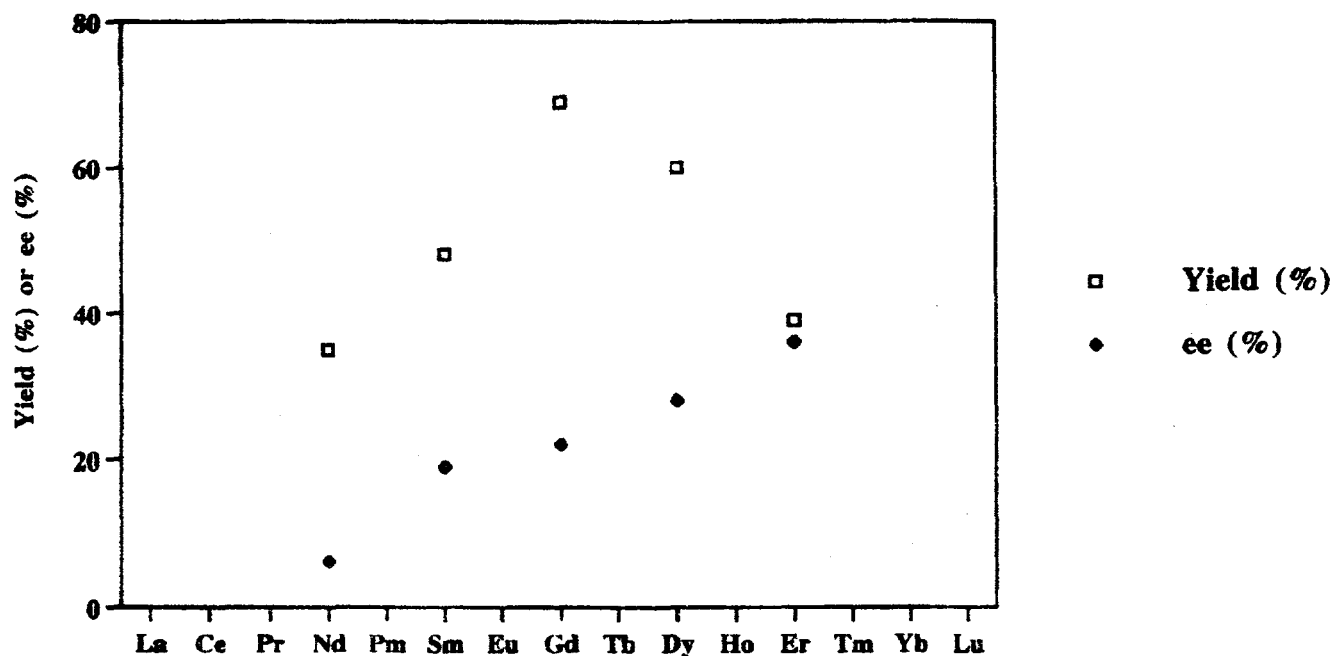


**Figure 4.** Plot of yields and enantioselectivities for MPV reduction of acetophenone employing Schiff-base ligand **1**.

It can be seen for ligand **1**, however, that enantioselectivity reaches a maximum when gadolinium is employed, whereas the yield is maximized when erbium is utilized. Plots such as these demonstrate the unique nature of the lanthanide elements - significant changes in reactivity can be observed simply by moving one or two elements to the right or left in the series (*i.e.* a catalyst may be "tuned" or optimized by selecting the appropriate metal center). In order to compare our results to those obtained with a commercially available Schiff-base ligand, lanthanide tris(amide) complexes were treated with one equivalent of Jacobsen's ligand (which was originally developed for asymmetric epoxidation reactions), and the resulting complex was used *in situ* as an MPV reduction catalyst of acetophenone:

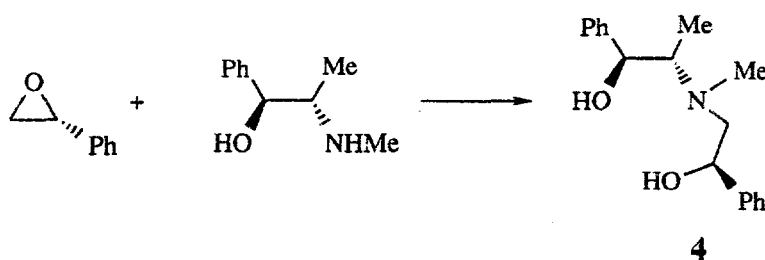






**Figure 5.** Plot of yields and enantioselectivities for MPV reduction of acetophenone employing Jacobsen's ligand.

We have also investigated the synthesis of amino-diolate ligands following the reaction of a chiral amino alcohol with a chiral epoxide. Thus the reaction of ephedrine with styrene epoxide produced N-(2-hydroxyphenethyl)ephedrine (**4**). One equivalent of this ligand was allowed to react with lanthanide tris(amides) and alkoxides and the resulting solutions were employed as catalysts for the Meerwein-Ponndorf-Verley reduction of acetophenone:



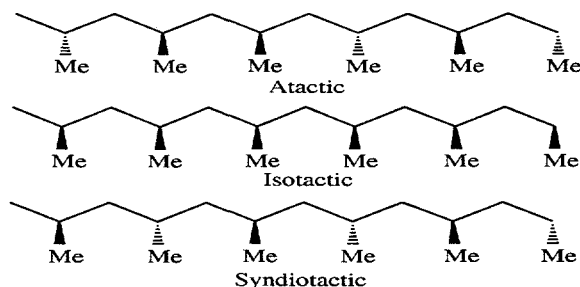
Conditions: 5 mol % catalyst, 2 ml THF, 0.25 ml *i*-PrOH, 24 h, room temperature.

Catalyst Precursor	Ligand	Yield (%)	ee (%)
Sm(O- <i>i</i> -Pr) <sub>3</sub>	<b>4</b>	50	12
Gd[N(SiMe <sub>3</sub> ) <sub>2</sub> ] <sub>3</sub>	<b>4</b>	98	0
[La(OCH <sub>2</sub> CMe <sub>3</sub> ) <sub>3</sub> ] <sub>4</sub>	<b>4</b>	98	2
[La(OAr) <sub>3</sub> ] <sub>2</sub>	<b>4</b>	98	22
NdI <sub>3</sub> + K <sub>2</sub> diolate	<b>4</b>	70	0

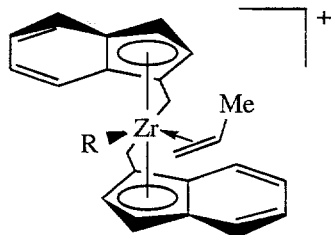
Enantioselectivities were again fairly low, although the reaction yields were very good. The additional flexibility in the backbones, when compared with the structurally similar Schiff-base ligands, may be responsible for the decline in selectivity.

Molecular modeling studies have been used to reveal potential designs for new chiral ligands. Thus the reaction of pyridine-2,6-dicarboxaldehyde with two equivalents of a cheap, chiral amino alcohol such as norephedrine, leads to the formation of a potentially pentadentate ligand, which molecular modeling studies suggest will very effectively chelate a lanthanide metal center to form a highly asymmetric environment. Catalytic studies of this ligand are currently in progress, together with a related hexadentate ligand prepared from 1,10-phenanthroline-2,9-dicarboxaldehyde and two equivalents of norephedrine.

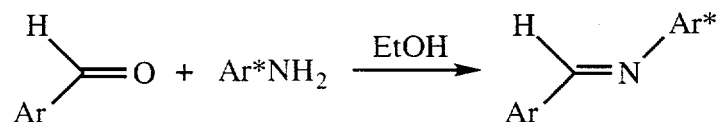
Our efforts to design new chiral ligands have also led into the field of stereospecific polymerization of prochiral olefins. In the industrial sector, the polymerization of propylene is one of the largest volume processes currently performed, and the production of highly stereoregular polypropylene is becoming extremely important. So-called "atactic" (or random) polypropylene, produced by a non-directing catalyst, is of limited commercial use and value. However, both "isotactic" and "syndiotactic" polypropylene, in which the methyl groups occupy the same side or alternating sides of the polymer chain (see below), possess far superior mechanical properties and are widely used in consumer products. In order to control the arrangement of methyl groups along a growing chain of polypropylene, the catalyst must exert a directing influence (*i.e.* it must be enantioselective).



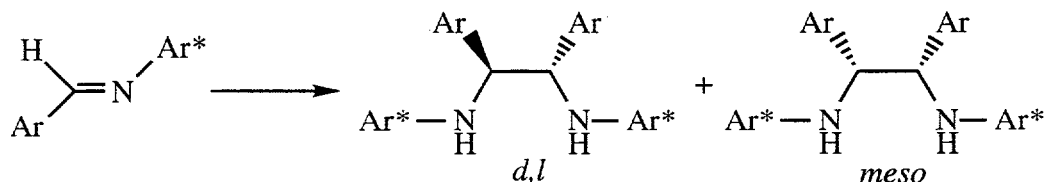
Currently, the best catalysts for performing this polymerization in a stereocontrolled manner contain two linked indenyl ligands that coordinate to the metal so as to produce a chiral environment:



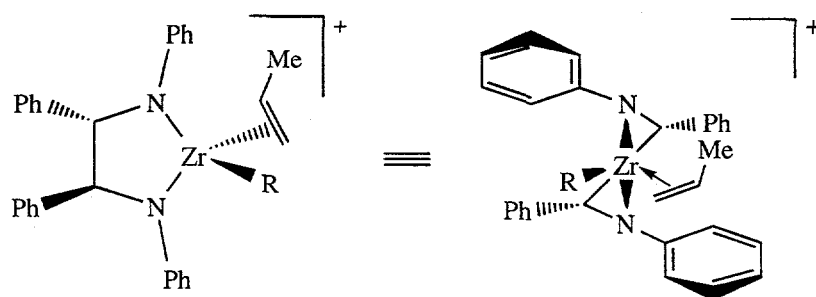
We have developed a new class of nonmetallocene ligands, which should be capable of supporting a catalytically-active metal center, and also of controlling the stereochemistry of a growing polymer chain. The synthetic procedure begins with the preparation of an aldimine, by the simple reaction of a substituted aniline with an aromatic aldehyde:



The second step of the synthesis is a reductive coupling reaction in that two equivalents of aldimine are coupled to form one equivalent of a 1,2-diamine. The coupling reaction results in the formation of two diastereoisomers - a *meso* isomer (which contains a mirror plane) and a *d,l* pair of enantiomers. For our purposes, the *d,l* enantiomeric pair would be of most use since it is this  $C_2$ -symmetric ligand that would give the correct stereocontrol over a polymer chain once it was attached to a metal center:



Attachment of this ligand to a metal center gives a catalyst, which should closely mimic the directing abilities of the bis-indenyl class of catalysts:



In the case of the diamine ligands, however, the nature of the group attached to the nitrogen atom may be readily altered simply by using a different substituted aniline during preparation of the aldimine. The groups on the two-carbon backbone may be similarly modified such that an extremely wide range of substituted diamine ligands may be prepared in order to optimize the performance of the catalyst. This ability to easily prepare a wide range of ligands that differ only in their substitution patterns is not available with the bis-indenyl ligands.

Our current efforts are being directed toward optimizing the coupling reaction of the aldimine ligands so that the reaction is successful for a wide range of substituents on both the aldehyde and aniline. We have also prepared a number of catalysts that contain a diamine ligand bridged by a single silicon atom rather than a two-carbon backbone. These catalysts have been shown to be effective for the polymerization of ethylene, and studies are currently underway with propylene and other substituted olefins.

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