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Preparation of Several Asymmetric Tridentate and Tetradentate Schiff-Base Ligands, Synthesis of Their Transition Metal Complexes and an Investigation of Application of Some Metal Complexes as Catalyst in Organic Reactions

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Dedicated to:

My dear ***parents***

My affectionate ***husband***

My compassionate ***brothers*** *and* ***sister***

And

My beloved son ***"Arash"***

I would also like to dedicate this dissertation to the noble departed spirit of the founder of Kerman Shahid Bahonar University, ***Mr. Alireza Afzalipour***

Acknowledgments:

Oh mighty God, the sole knower of all knowledge and creator of all secrets and mysteries, I thank you for bestowing on me the blessing of learning and insight. I beg you to lead me to a path in which I can make a worthy use of the knowledge I have acquired.

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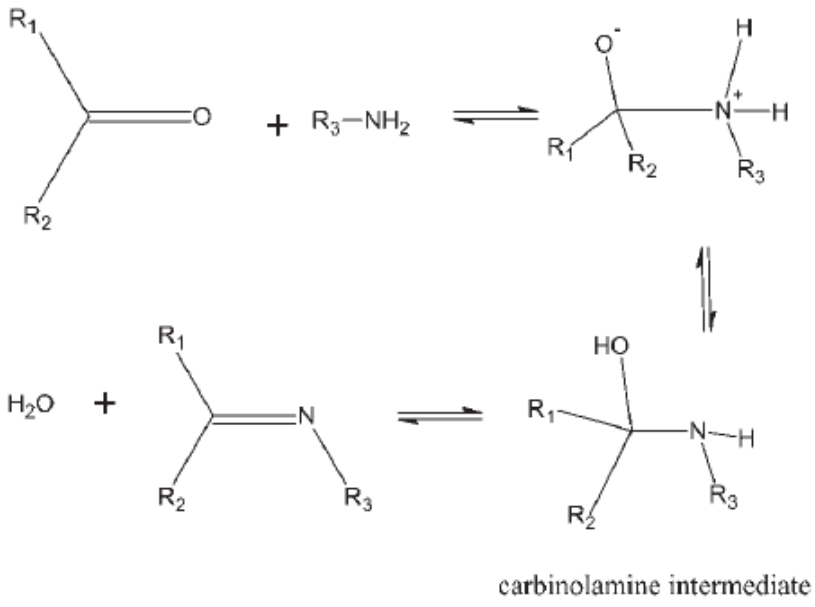
1.1. Introduction

Hugo Schiff described the condensation between an aldehyde and an amine leading to a Schiff base in 1864 (Scheme 1-1) [1]. Schiff base ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. Modern chemists still prepare Schiff bases, and nowadays active and well-designed Schiff base ligands are considered ‘‘privileged ligands’’. In fact, Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful catalytic transformations. From a practical point of view, the aspects involved in the preparation of Schiff base metal complexes are spread out in the literature. We wish to summarize and introduce some practical guidelines for the preparation and use of Schiff base metal complexes in catalysis.



(Scheme 1-1). General scheme for the formation of a Schiff base

A particular class of Schiff bases is discussed. When two equivalents of salicylaldehyde are combined with a diamine, a particular chelating Schiff base is produced. The so-called Salen ligands, with four coordinating sites and two axial sites open to ancillary ligands, are very much like porphyrins, but more easily prepared. Although the term Salen was used originally only to describe the tetradentate Schiff bases derived from

ethylenediamine, the more general term Salen-type is used in the literature to describe the class of [O,N,N,O] tetradentate bis-Schiff base ligands (Fig.1-1).

Basic guidelines for the design, synthesis and application of metal Schiff base complexes in catalysis will thus be surveyed with the emphasis on the relevant problems in producing active and useful complexes.

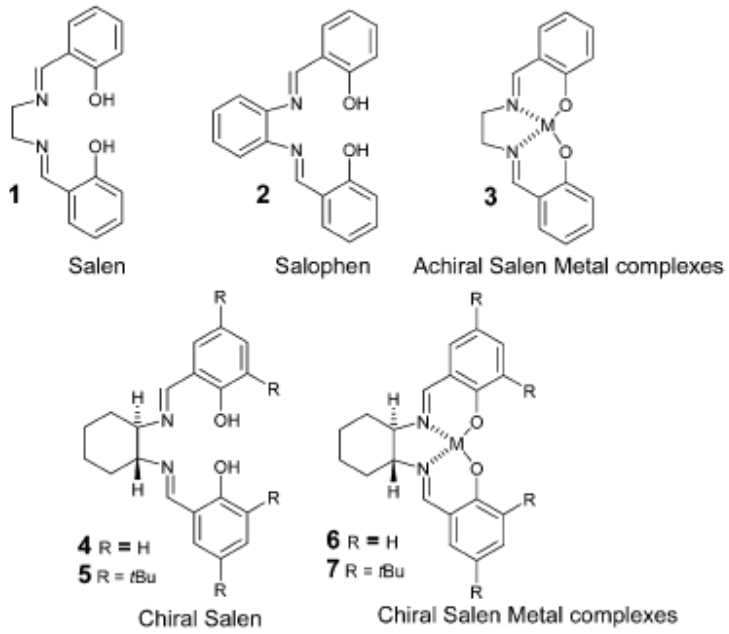


Fig. 1-1 Different Salen ligands and M(Salen) complexes.

1.1.1. Preparation of Schiff bases

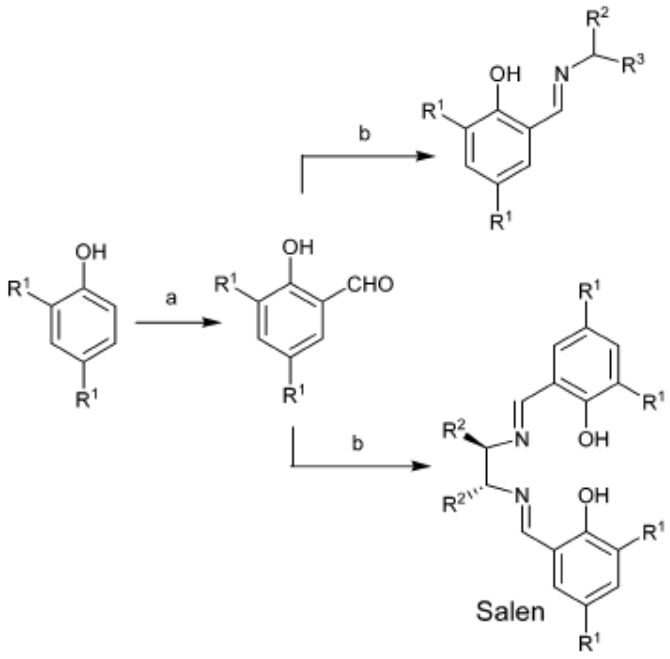
Condensation between aldehydes and amines is realized in different reaction conditions, and in different solvents. The presence of dehydrating agents normally favors the formation of Schiff bases. $MgSO_4$ is commonly employed as a dehydrating agent.

The water produced in the reaction can also be removed from the equilibrium using a Dean Stark apparatus, when conducting the synthesis in toluene or benzene. Finally, ethanol, at room temperature or in refluxing conditions, is also a valuable solvent for the preparation of Schiff bases. Degradation of the Schiff bases can occur during the purification step. Chromatography of Schiff bases on silica gel can cause some degree of decomposition of the Schiff bases, through hydrolysis. In this case, it is better to purify the Schiff base by crystallization. If the Schiff bases are insoluble in hexane or cyclohexane, they can be purified by stirring the crude reaction mixture in these solvents,

sometimes adding a small portion of a more polar solvent (Et_2O, CH_2Cl_2), in order to eliminate impurities. In general, Schiff bases are stable solids and can be stored without precautions. Condensation of salicylaldehydes or salicylaldehyde derivatives with 1, 2-diamines leads to the formation of one extremely important class of ligands, generally known as ‘‘Salens’’ (Fig. 1-1). Salicylaldehydes bearing different substituents are obtained by the introduction of a formyl group, using a simple and well established reaction, into the corresponding phenol derivatives (Scheme 1-2, a).

The combinatorial approach to the discovery of new catalysts is an innovative and exciting area of research.[2]

Schiff bases are suitable ligands for the preparation of libraries due to the easy reaction conditions and the variety of chiral amines and aldehydes used as precursors. Amino acids and peptides are particularly suitable for the creation of effective catalysts, as indicated in the research of Hoveyda and Snapper.[3] The condensation of aldehyde-bearing coordinating groups with amino acids and peptides provides interesting Schiff bases, used to make a combinatorial library of ligands.[2]



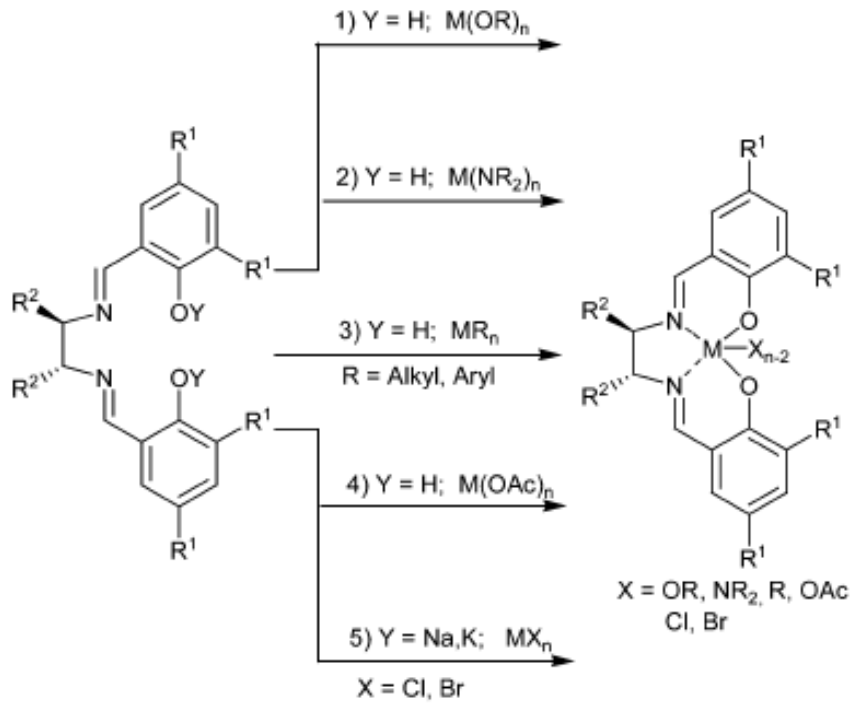
(Scheme 1-2). Preparation of Schiff bases

1.1.2. The complexation steps: different routes

Essentially, five different synthetic routes can be identified for the preparation of Schiff base metal complexes (Scheme 1-3).[4]

Route 1 involves the use of metal alkoxides, M(OR)n . For early transition metals (M = Ti, Zr), alkoxide derivatives are commercially available and easy to handle, while the use of other alkoxide derivatives is more problematic, particularly in the case of highly moisture-sensitive derivatives of lanthanides. The reaction of a Schiff base with a metal alkoxide is an equilibrium reaction and the identity of the species generated is sometimes difficult to predict. Different complexes can be present in different concentrations, as a function of the equilibrium constant. However, the introduction of a bulky group in the Schiff bases can control the identity and homogeneity of the complex, by shifting the equilibrium towards the formation of a single species. Metal alkoxides are sensitive to hydrolysis and the presence of adventitious water can result in the formation of μ-oxo species. Additionally, metal Schiff bases bearing alkoxide groups as ligands, are sensitive to traces of water, producing various μ-oxo species. The presence of adventitious water is difficult to control, especially when the reaction between the Schiff bases and the metal alkoxide is performed in situ. The formation of μ -oxo species can cause difficulties in reproducing the results of catalytic reactions.

Metal amides $M(NMe_2)_4$ (M = Ti, Zr) are also highly suitable precursors for the preparation of Schiff base metal complexes of early transition metals. The reaction occurs via the elimination of the acidic phenolic proton of the Schiff bases, occurring at the same time as the formation of volatile $NHMe_2$. The reaction of Ti $(NMe_2)_4$ or $Zr(NMe_2)_4$ with Salen gives a Schiff base metal complex bearing two bisamido groups that can be reacted further. The reaction of the bisamido Salen complex with Me_3SiCl transforms the bis-amido into the bis-chloride complex.



(Scheme 1-3). Preparation of Schiff base complexes

A Schiff base metal complex can be prepared in a clean and effective way using metal alkyl complexes as precursors (route 3). Various metal alkyls in the main group of metals ($AlMe_3$, $GaMe_3$, and $InMe_3$) are commercially available and can be used in the preparation of Schiff bases by a direct exchange reaction. In this context, particularly suitable for the synthesis of iron, manganese, vanadium and copper Schiff bases are the corresponding $M(Mesityl)_n$ (M = Fe, Mn, V, Cu, Mesityl=2,4,6-trimethylbenzene) compounds. They are obtained from the reaction of the corresponding metal halides with a mesityl Grignard reagent. This reaction only liberates a by-product, 1, 3, 5-trimethylbenzene (mesitylene). Although the synthesis of mesityl metal complex precursors can be difficult due to their sensitivity, their use can avoid the presence of an uncharacterized impurity or the formation of binuclear complexes. Alkyl titanium and zirconium tetrabenzyl alkyl complexes are used in the preparation of Schiff base metal complexes that are active as polymerization catalysts. These alkyl reagents are obtained from titanium and zirconium halides by the reaction of a benzyl Grignard reagent.

As indicated in route 4, many Schiff base metal complexes can be obtained through the treatment of the Schiff base with the corresponding metal acetate, normally by heating

the Schiff base in the presence of the metal salt under reflux conditions. Copper, cobalt and nickel Schiff bases are prepared using the corresponding acetate M $(OAc)_2$ (M = Ni, Cu, Co). Instead of using acetate, a direct exchange with metal halides is also possible. In fact, early transition Schiff bases are sometimes prepared by direct reaction with $TiCl_4$ or $ZrCl_4$. All the methods presented (routes 1–4) are used for Schiff bases or Salen metal complexes.

The synthetic scheme presented in route 5 is quite effective in obtaining Salen metal complexes. It consists of a two-step reaction involving the deprotonation of the Schiff bases and a successive reaction with metal halides. Deprotonation of the acidic phenolic hydrogen can be realized using lithium bases (MeLi, BuLi). However, since lithium alkyls can attack the imine group of the Schiff base, it is advisable to perform the deprotonation step with NaH or KH in coordinating solvents. The deprotonation step is normally rapid at room temperature, but heating the reaction mixture to reflux does not cause decomposition. Use of excess NaH and KH is recommended, when the Na and K Salen obtained are soluble in the reaction solvent. THF is the solvent generally used for this type of preparation, and the sodium or potassium hydride used in excess can be eliminated by filtration, when the formation of the Na_2(Salen) or K_2(Salen) is complete. The reaction scheme is quite general, and metal halides other than titanium and lanthanides could be used. Instead of adding the metal halides to the reaction mixture, the use of available tetrahydrofuranyl adducts, such as $TiCl_4(THF)_2$, $ZrCl_4(THF)_2$, or $VCl_3(THF)_3$, is more effective. When not commercially available, the tetrahydrofuranyl adducts of metal halides are easily prepared by the addition of THF to metal halides in a different solvent, normally CH_2Cl_2. Tetrahydrofuranyl adducts are moderately sensitive salts, and can rapidly be handled freely in air. However, in the case of the more sensitive $VCl_3(THF)_3$ and $TiCl_3(THF)_3$ this procedure is not recommended. When large amounts of Salens are available, performing the synthesis on a large scale could be recommended using route 5. However, this synthetic strategy can create problems in the purification steps, during the isolation of the Schiff base metal complex. The reaction of Na_2(Salen) or K_2(Salen) with metal halides generates sodium or potassium salts as by-products. Generally, the formation of the Salen metal complex via route 5 is performed in THF and the insoluble sodium or potassium halides obtained as by-products can be eliminated by

filtration. However, as the oxygens of the M(Salen) are Lewis basic centers, coordination of sodium or potassium halides could result, leading to many problems in the purification of the Schiff base metal complexes. For catalytic purposes, when synthesis is performed in situ by route 5, the presence of coordinated salts can alter the catalytic performance of the Schiff base metal complexes.[4]

1.1.3. Substitution and conformational effects in Schiff bases

Coordination of the metal with bi- or tridentate Schiff bases can produce dimeric, or a saturated metal complex. Particularly with early transition metals, which have a tendency to coordinate ligands in an octahedral manner, the complexation step realized in situ can produce a saturated octahedral complex. When chiral Schiff bases are used in the catalytic process, the formation of a saturated inactive complex is detrimental to catalysis. The formation of stable or saturated complexes is, of course, a factor of lack of efficiency in the catalytic process. The introduction of bulky substituents near the coordination sites can eliminate this problem and enhance the catalytic performance of the Schiff base metal complex, thus preventing the early transition Schiff base complexes from forming stable and catalytically inert octahedral complexes. Metals coordinated to Schiff bases can transmit chiral information via the coordination of the electrophile to the Lewis acidic center, or via an activation of the nucleophile. Metal Salen complexes have the unusual characteristic of activating, in certain reactions, both the nucleophile and the electrophile. In the transfer of carbene, nitrene or oxene (Fig. 1-2), the structure of Salen influences the incoming trajectory of the substrate and its orientation. Although stereogenic centres are normally placed in the diamine moiety, subtle conformational effects transfer the chiral information. M(Salen) can adopt different conformations, as shown by crystallographic studies.

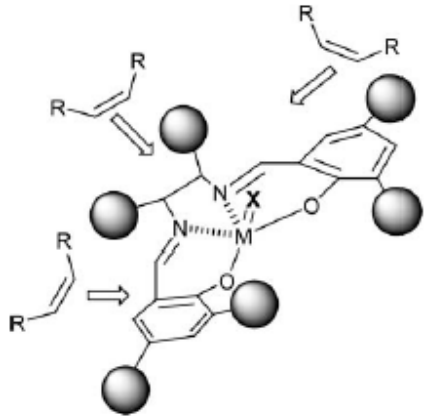


Fig. 1-2 Different approaches of a substrate to the Salen complex.

While a few M(Salen) complexes show planar conformations, most of the examples reported in the literature show a bowl (or umbrella, Fig. 1-3A) conformation, and a stepped non-planar conformation is also assumed by the complex in the solid state (Fig. 1-3B).

Fig. 1-3 Different shapes of Salen complexes.

In the stepped conformation, the degree of folding is correlated to the size of the metal, its oxidation state, the absence or presence of apical ligands, and the nature of the substituent. Cr(V)(Salen) is folded, while the corresponding Cr(III)(Salen) is near planar.[5] The conformation of Salen in the particular oxidation state influences the trajectory of approach of the incoming substrate. Therefore, bulky groups on the aromatic aldehyde do not block the approach but regulate the orientation of the incoming substrates, determining a high diastereofacial preference.When different elements of chirality's are present in the same ligand, the conformational effects are more pronounced. This is the case for the Salen described by Katsuki[5] (Fig. 1-4).

Fig. 1-4 The second generation of Salen.

M(Salen) like **8** and **9**, with a chiral binaphthyl or similar structure, belong to the second generation of M(Salen). M(Salen), when different chiral elements are not combined, belongs to the first generation. The ligand conformation in Fig.1-4, where a binaphthyl unit is combined with diamine containing stereogenic centers, is dictated by at least two factors. The combination of stereogenic elements controls the folding. The binaphthyl ligands bring an aryl group close to the metal.

The polar π-interactions occurring between the aryl group and an apical ligand, usually water, can act synergistically with a folding effect. The folding effect, deriving from the conformation imposed by the chelating diamine moiety, is thus enhanced in these Salens, compared to other Salen metal complexes. On the other hand, these effects can act conversely, reducing the folding. In general, the fact of the absence of an axial coordinating ligand can either reduce or enhance the folding of the metal complex. This is important for the transmission of chiral information. Theoretical calculations have shown that axial donor ligands, which change the conformation of the catalyst, bring the metal closer to the substrate in rate determining stereoselective processes, enhancing the enantioselectivity (Fig. 1-5).

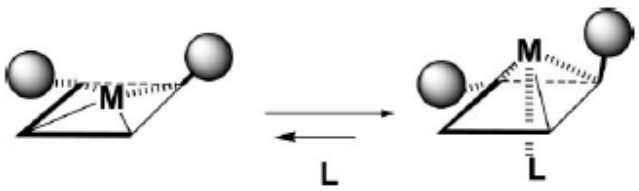


Fig. 1-5 Effect of an axial ligand on the Salen complex.

1.2. Some kinds of metal Schiff bases

1.2.1. Chiral Schiff bases of early transition metals

The Ziegler–Natta catalyst was originally based on the combination of $TiCl_4$ with alkylaluminium, and it was soon discovered that $MgCl_2$-supported titanium was more stable and more active. The break through, due to the introduction of group 4-metallocene as a well-defined metal complex, in combination with partially hydrolyzed trimethylaluminium(methylalumoxane, MAO), has made the industrial application of these catalysts possible. Soon it was realized that a system able to mimic the coordination properties of metallocene would be able to perform polymerization as well. In this context Schiff bases were widely used, because they can control the coordination properties of the metal and form a coordination environment, similar to a metallocene (Fig. 1-6).

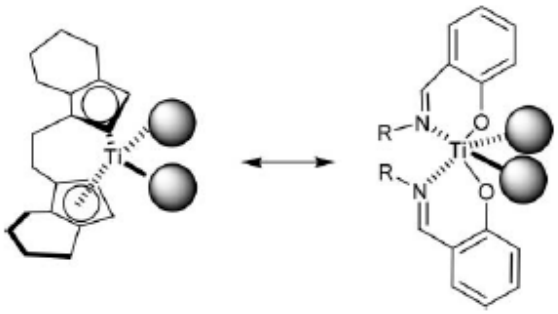


Fig. 1-6 Formal equivalence between indenyl complexes and Schiff bases.

In fact, Schiff bases possess many interesting characteristics. They are moderate electron donors, with a chelating structure and a low electron counting number. In addition, a large library of Schiff bases can easily be generated, with structural diversity, both sterically and electronically. Schiff base complexes of early transition metals are active catalysts for polymerization, provided that some simple criteria in the synthetic design are met.[6]

The coordination of phenoxy-imine to zirconium and titanium displays a distorted octahedral structure, with two nitrogen atoms and two chlorine atoms in *cis* position. It is important to realize that several isomers are possible, and the stability and reactivity are functions of the substituents of the Schiff bases. The introduction of bulky groups in the

phenoxy ring near to the oxygen is important, in order to stabilize these Schiff bases and make them synthetically useful for polymerization. Interestingly, the octahedral and C_2-symmetric Ti- and Zr-bis(phenoxyimine) complexes are chiral at the metal, with the titanium assuming a fluxional Λ or Δ configuration (Fig. 1-7).

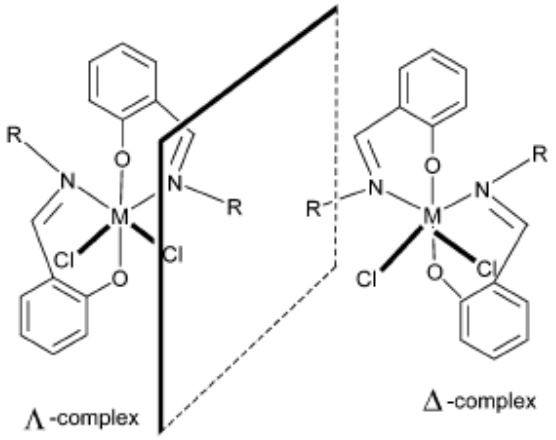


Fig. 1-7 A fluxional octahedral Schiff base complexes.

Although the rapid exchange in the polymerization process is beneficial to stereocontrol, the formation of different diastereoisomers can cause low stereocontrol in other reactions, especially if stereogenic centers are inserted in the ligands. For this reason, the chiral Schiff bases employed in catalysis with early transition metals have been designed specifically to avoid the problem. Two solutions have been indicated by various authors in the course of their studies on the use of Schiff base early transition metal complexes:

a) The use of tridentate or tetradentate Schiff bases;

b) The use of Salen as a rigid tetradentate coordinating framework.

Tridentate Schiff base ligands have been used successfully in several asymmetric catalytic reactions. In this type of catalysis, the size of the substituents on the periphery of the ligand plays a key role in determining the enantiomeric excess of the product. The reaction with $Ti(O^iPr)_4$ and Schiff base ligands is clean only if the R_1 group is bulky (Scheme 1-3). When R_1 is not bulky, two ligands can coordinate titanium, even if it is present in stoichiometric amounts. Thus, the reaction between a tridentate ligand and $Ti(O^iPr)_4$ can give three different isomers. A t-butyl group is normally sufficient to