

Stereoselective synthesis with zirconium complexes

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Abstract - Two types of electrophilic zirconium based catalyst systems are described in several variants. The organometallic Lewis acid CpZrCl_3 is easily available. It catalyzes a variety of organic reactions quite selectively. Starting from the camphor enantiomers the chiral Lewis acid (diborna-Cp)ZrCl₃ was prepared. It catalyzes the enantioselective ortho-hydroxylation of α -naphthol. In separate experiments the enantiomeric α -naphthol/ethylpyruvate addition products were obtained on a preparative scale with $\geq 85\%$ ee using 1 to 5 mol% of the optically pure (+) or (-)(diborna-Cp)zirconium trichloride catalyst, respectively. Bis(cyclopentadienyl)zirconium dihalides (R^*Cp)₂ZrCl₂ bearing chiral substituents at the Cp-rings were used for generating homogeneous group 4 metallocene/alumoxane Ziegler catalysts for the stereoselective polymerization of propene. Systematic variation of substituents at the chiral Cp-side chains revealed a substituent additivity effect of the stereoselective CC-coupling process. Non-bridged bis(1-alkylindenyl)zirconium complexes exhibiting planar chirality can very easily be prepared optically pure in an asymmetric organometallic synthesis using terpene- or steroid-derived indenyl substituents. Some of these complexes produce homogeneous Ziegler catalysts that are nearly as stereoselective propene polymerization catalysts as the commonly used ansa-metallocene complexes. Bis(isopropylcyclopentadienyl)titanium dichloride/alumoxane is an achiral organometallic catalyst system that produces isotactic block polypropylene at -50°C by means of chain end control. At $+10^\circ\text{C}$ this is changed to slightly syndiotactic polymer formation. A reaction scheme is proposed that may account for the observed linear $\lg \sigma/(1-\sigma)$ vs $1/T$ relationship observed for this specific catalyst system.

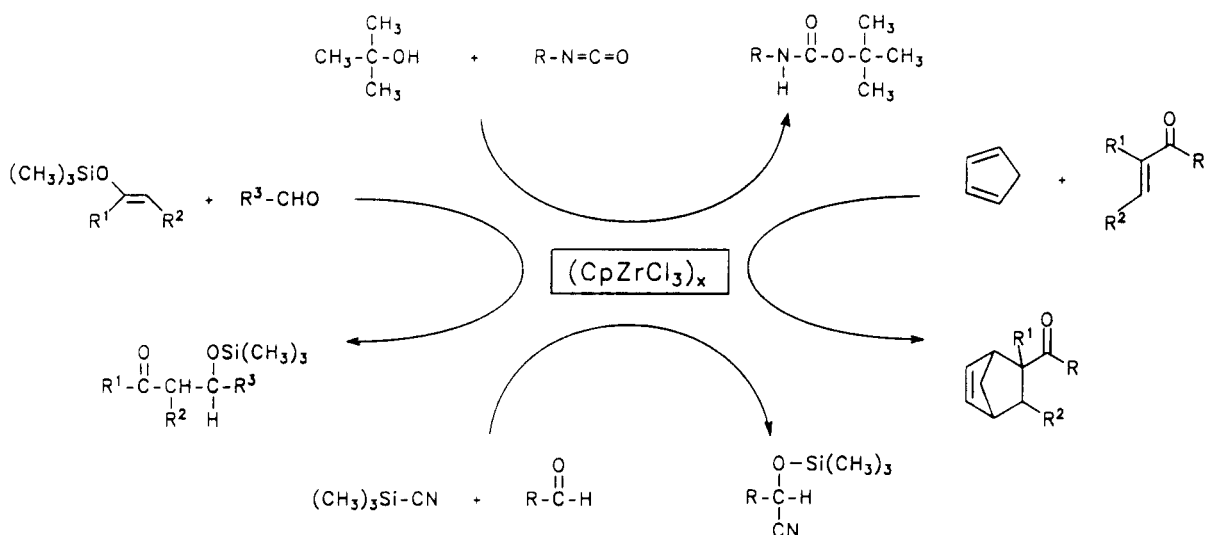
INTRODUCTION

Organometallic reagents have become of increasing importance for carrying out selective transformations of organic compounds. Numerous extremely efficient stoichiometric applications of organometallics in organic synthesis have been reported in the literature. I think that we are currently at the onset of developing the use of organometallic compounds in synthetic organic chemistry one step further, namely by selectively catalyzing an increasing number of various types of organic transformations by means of specifically designed catalyst systems derived from structurally well characterized molecular metal complexes. This concept is already being used extensively for a selected number of reaction types, very often employing catalyst systems containing electron rich late transition metals. In addition the oxophilic early transition metals have become of increasing importance lately being used in catalyst systems for e.g. stereoselective oxidation or carbon carbon coupling reactions. I would like to present several examples from my group where we have contributed to the use of zirconium derived metal complexes as electrophilic (i.e. Lewis acidic) catalysts inducing selective CC bond formation.

The zirconium catalysts used for this study all contained η -cyclopentadienyl ligands. They are in one way or another derived from bis(η -cyclopentadienyl)zirconium dihalides. The $d^0/16$ -electron Cp_2ZrX_2 species itself is usually not electrophilic enough to serve as a reactive organometallic Lewis acid catalyst for CC-coupling reactions. Therefore, we have used two ways for increasing electrophilicity. Formal X^- removal led to Cp_2ZrR^+ complexes; in situ generated they serve as the active species for very rapid olefin coupling processes (homogeneous Ziegler catalysts). Alternatively, replacement of a Cp-ligand for chloride yields CpZrCl_3 which has turned out a versatile Lewis acid catalyst for selective organic transformations.

ORGANOMETALLIC CpZrCl_3 -DERIVED LEWIS ACID CATALYSTS

The parent compound in this series, mono(η -cyclopentadienyl)zirconium trichloride, can readily be prepared and obtained very pure even in large quantities by a radical chain chlorination of Cp_2ZrCl_2 (ref. 1). CpZrCl_3 is an insoluble Cl-bridged oligomer (ref. 2) which readily dissolves in common organic solvents upon the addition of a wide variety of donor ligands. It catalyzes a number of organic reactions

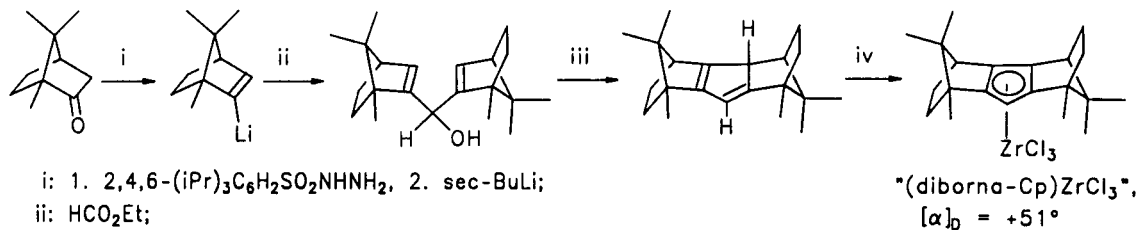


susceptible to general Lewis acid catalysis, such as the Diels-Alder reaction, hydrosilylation or cyanosilylation of organic carbonyl compounds, aldol type CC-coupling reactions or the addition of hindered tert. alcohols to isocyanates to give protected amines (ref. 3).

The use of the organometallic CpZrCl_3 catalyst is often advantageous over the common inorganic Lewis acids (such as BF_3 , AlCl_3 or TiCl_4) because reactions proceed cleaner and are sometimes more selective. The Diels-Alder addition of methacrolein to 2,3-dimethylbutadiene is a typical example. The thermally induced 1,3,4-trimethylcyclohexenylcarbaldehyde formation requires a temperature of 150°C . TiCl_4 or SnCl_4 catalysis induces the CC-coupling reaction at room temperature but very effectively catalyzes the rapid subsequent rearrangement of the primary cyclohexenylcarbaldehyde product to give 1,3,4-trimethylbicyclo[2.2.1]heptan-2-one (ref. 4). In contrast, CpZrCl_3 , employed as the soluble bis thf adduct (5 - 10 mol%), very effectively catalyzes the formation of the simple [4+2]-cycloadduct at ambient conditions without any further isomerization reaction (ref. 3).

As another typical example, we looked at the Lewis acid catalyzed orthoselective hydroxyalkylation of hydroxyarenes in some detail. The reaction of α -naphthol with ethylpyruvate in the presence of one molar equivalent of CpZrCl_3 gave the hydroxyalkylated reaction product O-coordinated to zirconium in good yield. Apparently, the hydroxyarene had added to the CpZrCl_3 -system with loss of HCl. Then the reactive carbonyl component was coordinated and the aldol type carbon carbon bond formation had taken place in the coordination sphere of the transition metal, followed by (probably catalyzed) hydrogen shift. The thus formed product complex very effectively catalyzed the α -naphthol plus ethylpyruvate ortho-hydroxyalkylation reaction. Since this reaction product contained a chiral center we looked for ways to develop this CC-coupling process, which was very effectively and cleanly catalyzed by the achiral organometallic mono(cyclopentadienyl)zirconium Lewis acid system, into an enantioselective catalytic reaction (ref. 5).

A new chiral cyclopentadienyl ligand was prepared starting from 1R,4R-camphor. Transformation into the alkenyl lithium reagent was achieved by means of the Shapiro reaction. Then followed its addition to 1/2 molar equivalent of methyl formate. Acid catalyzed dehydration and ring closure gave the substituted cyclopentadienyl system (two diastereomers). Deprotonation was achieved with *n*-butyl lithium and the subsequent reaction with zirconium tetrachloride gave "(diborna-Cp) ZrCl_3 " enantiomerically pure ($[\alpha]_D = +51^\circ$) (ref. 5). Its enantiomer was synthesized separately starting from 1S,4S-camphor.



i: 1. 2,4,6-(*i*Pr) $_3$ C $_6$ H $_2$ SO $_2$ NHNNH $_2$, 2. *sec*-BuLi;

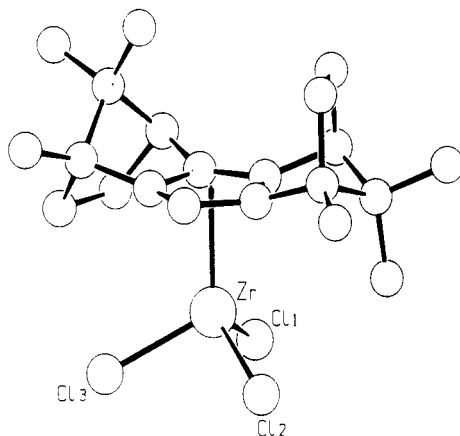
ii: HCO $_2$ Et;

iii: KHSO $_4$, 100-150 $^\circ\text{C}$;

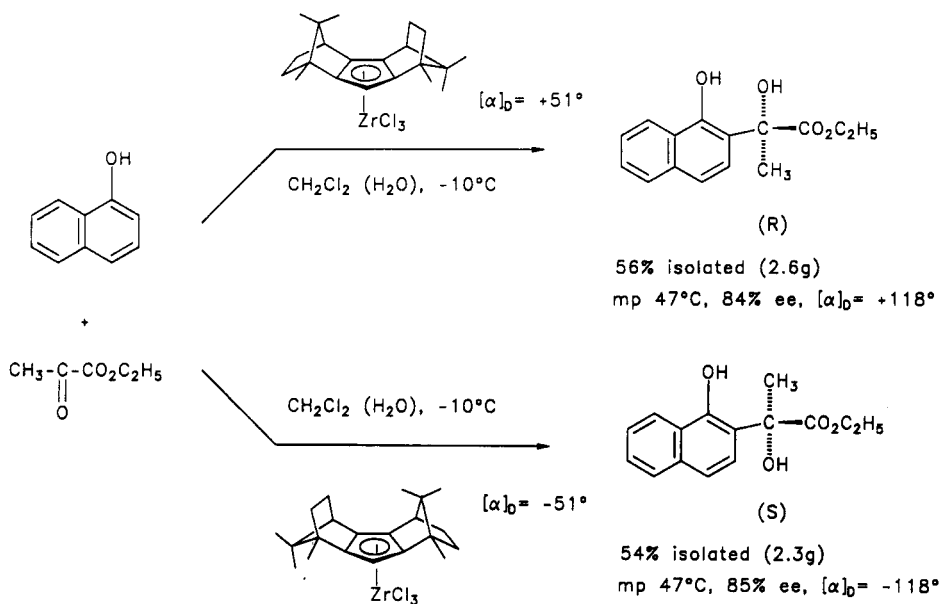
iv: 1. *n*-BuLi, Et $_2$ O, 2. ZrCl $_4$.

"(diborna-Cp) ZrCl_3 ",
 $[\alpha]_D = +51^\circ$

The (+)(diborna-Cp)ZrCl₃ enantiomer was characterized by an X-ray crystal structure analysis. A view of the molecular geometry is shown below. In contrast to the many CpZrCl₃L₂ complexes characterized by X-ray diffraction (ref. 3), which all exhibit distorted octahedral coordination geometry at zirconium, the early metal in (diborna-Cp)zirconium trichloride is tetrahedrally coordinated to the substituted Cp-ring system and three chloride ligands. This clearly underlines the severe steric bulk exhibited by the η⁵-(diborna-Cp) ligand system in this chiral organometallic Lewis acid.



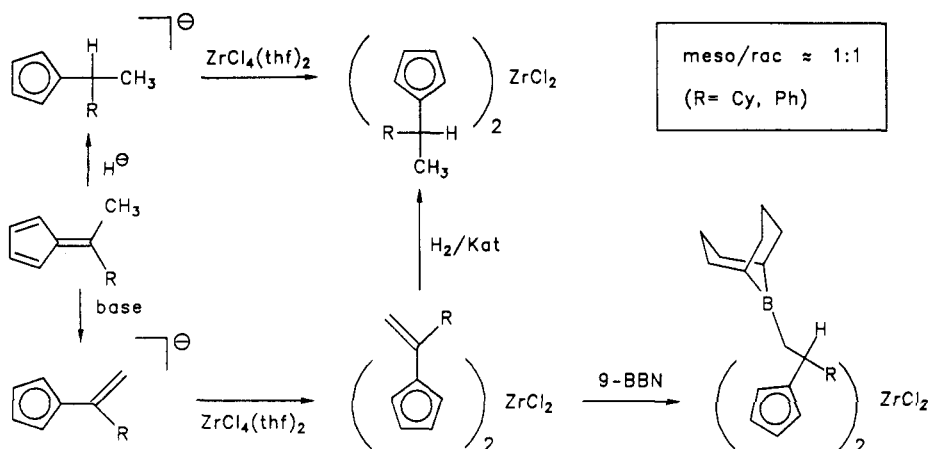
We employed the (diborna-Cp)ZrCl₃ enantiomers as catalysts for the enantioselective ortho-hydroxyalkylation of α-naphthol, using various pyruvates and pyruvate analogues RCOCO₂R' as reagents. With catalyst concentrations of 1 to 5 mol% a generally rather high enantiomeric excess (>80% ee) was achieved in all cases at low product conversions. Degradation and derivatization revealed that the 1R,4R-camphor derived (diborna-Cp)ZrCl₃ catalyst enantiomer produced the R-configured CC-coupling product. It turned out that catalyst stability was a problem in this asymmetric catalysis. For especially that reason some optimization of the reaction conditions was called for before this process could be used for practical synthetic purposes (ref. 6). We found out that during the catalytic reaction a small amount of the chiral catalyst was degraded by means of diborna-CpH removal after protonation of the ligand. This resulted in the generation of small quantities of very reactive achiral Lewis acid catalysts in the system, causing the formation of increasing amounts of racemic product with increasing conversion of the starting materials. This problem was satisfactorily overcome by increasing the pyruvate and catalyst concentrations to make the overall reaction faster. However, quite acceptable results for synthetic purposes were only achieved by adding a specific scavenger for the undesired reactive achiral Lewis acid formed in small amounts in this system. Water served this purpose extremely well, probably removing the trace amounts of ZrCl₄ or ZrCl₃OR formed by μ-oxobis(zirconium) complex formation. After the addition of substoichiometric H₂O quantities the enantiomeric excess of the hydroxyalkylated products was reproducibly >80% at >95% conversion on a preparative scale.



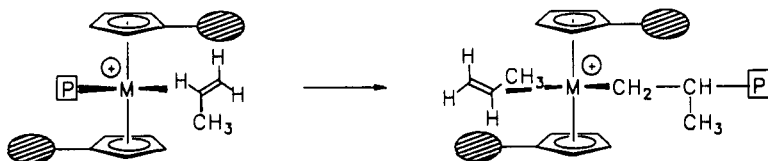
ZIRCONOCENE DERIVED HOMOGENEOUS ZIEGLER CATALYSTS FOR THE STEREOSELECTIVE PROPENE POLYMERIZATION

More than a decade ago Sinn and Kaminsky showed that group 4 metallocene halides can be activated by an excess of oligomeric methylalumoxane (AlMeO)_x to give extremely active homogeneous catalyst systems for the polymerization of α -olefins (ref. 7). This principle applied to Brintzinger's chiral (racemic) ansa-metallocene complexes (for examples see below) opened a new way for the stereoselective polymerization of prochiral α -olefins such as propene (ref. 8,9). In principle, chiral non-bridged bent metallocene complexes should be suitable precursors for the generation of stereoselective propene polymerization catalysts as well. It has been shown that attaching a substituent of sufficient steric bulk (usually \geq sec. alkyl) at each Cp-ring results in the chiral metallocene conformers being energetically favoured over the achiral (e.g. C_{2v}-symmetric) conformational alternatives. The overall chirality features of the bent metallocene may then be described by a helical chirality descriptor.

We have prepared a variety of such zirconium based systems, exhibiting at each cyclopentadienyl moiety a substituent containing a single chirality center (ref. 10). The complexes were synthesized by a combination of known steps starting from various 6-methylfulvene derivatives. The [Cp-CH(CH₃)R]₂ZrCl₂ (R = cyclohexyl or phenyl) complexes were easily available by hydrogenation of the respective (alkenyl-Cp)₂ZrCl₂ precursors. A hydroboration reaction produced the analogous complexes containing the very bulky -CH₂-(9-BBN) group attached to the chiral carbon center α to the Cp-ring system (ref. 11). In each case a near to equimolar mixture of the respective meso- and racem-diastereoisomers was obtained which were separated by fractional crystallization (ref. 10).



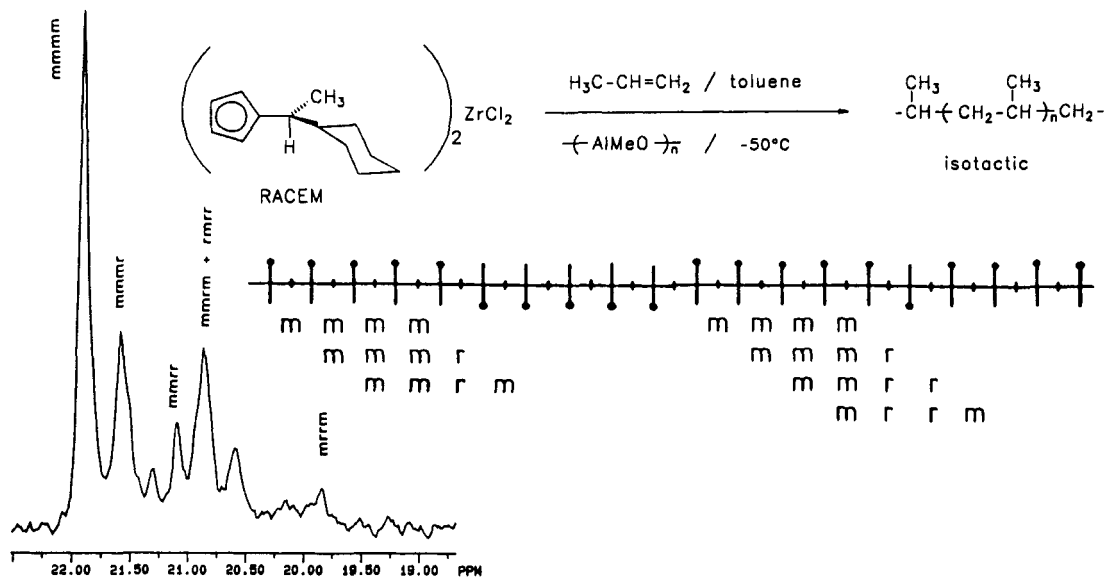
The chiral metallocene complexes were then converted to the catalytically active alkylzirconocenyl cation species by treatment with methylalumoxane according to the literature procedure (ref. 7-9). The chiral metallocene backbone can direct the stereochemically selective coordination of the propene monomer provided its chirality information is persistent on the time scale given by the chain propagating insertion/coordination reaction sequence. In the special cases looked at the otherwise adverse influence of the rapid metal-Cp rotation (leading to equilibration of the respective enantiomeric metallocene rotamers) is here overcome by attaching two homochiral substituents to the Cp-rings, thus making the metallocene rotational conformers diastereomeric.



There remains an additional complication on the way of effectively transferring the metallocene chirality information onto an organic carbon carbon coupling product, namely that metallocene chirality transfer ("enantiomorphic site control") is competing with (or at least is not independent of) the newly formed chiral carbon center at the end of the growing polymer chain influencing the re-/si-face orientation of the incoming olefin ("chain end control") (ref. 9, 10).

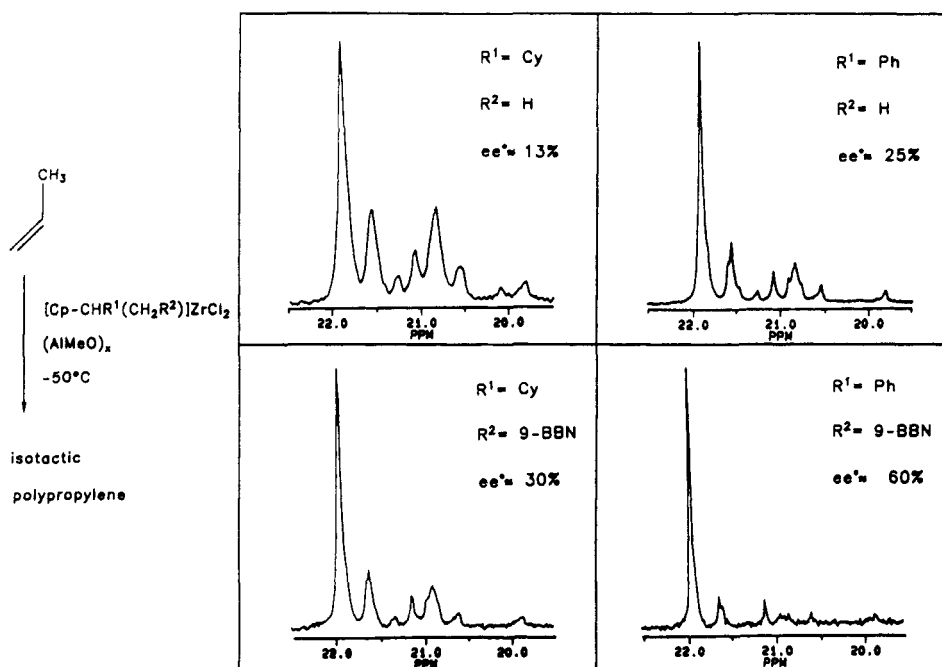
Fortunately, the consequences of these two dependent stereochemical influences can be analyzed and calculated apart in the case of polypropylene by means of a ¹³C NMR pentad analysis of the polymer methyl resonances combined with a statistical treatment (ref. 10, 12). For isotactic polypropylene, the dominant ¹³C NMR methyl resonance originates from the stereoregular mmmm pentad. Enantiomorphic

site control leads to singular stereochemical "mistakes" along the polymer chain. These give rise to additional signals of the mmmr, mmrr, and mrrm pentads in a 2:2:1 ratio, all being observed at lower δ values from the mmmm singlet. In contrast, chain end control leads to propagation of an inverted propene incorporation and this results in the formation of isotactic block sequences along the polymer chain. This becomes evident from a different NMR pattern (mmmr and mrrm in a 1:1 ratio) reflecting the altered type of the defect structure.



The racem-[Cp-CH(CH₃)cyclohexyl]₂ZrCl₂/methylalumoxane catalyst produces an isotactic polypropylene at -50°C with a (non-optimized) activity of 150 g of polymer / g [Zr] · h. The ¹³C NMR pentad analysis reveals that the dominating stereochemical control is due to the influence of the chain end. In this case, the effectiveness of transfer of the chirality information from the chiral metal center (or, more precisely, from the chiral metallocene backbone as discussed above) is only ee* = 13%.

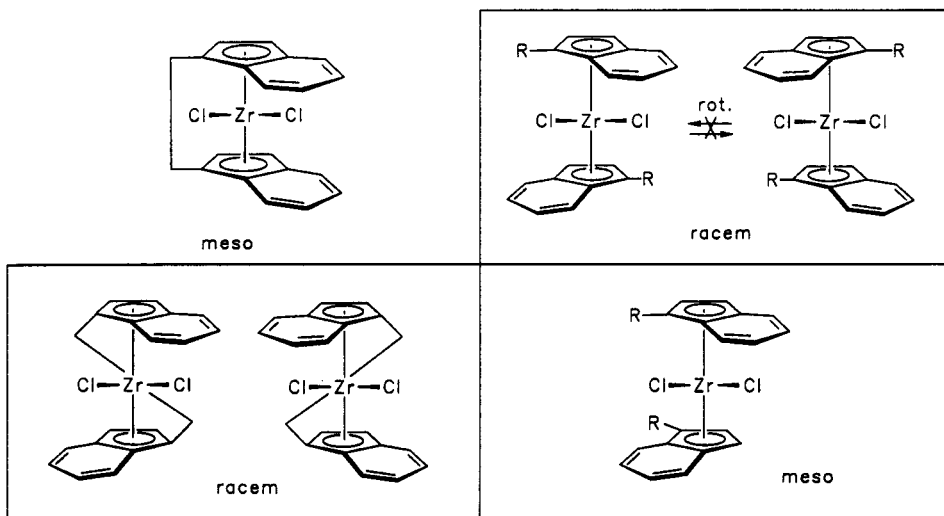
For optimization we have carried out a systematic variation of substituents at the Cp-side chain and have for some combinations found a near to additive substituent effect of ee*. This may be illustrated for the following selected series of examples. Starting from the (AlMeO)_x/[Cp-CH(CH₃)cyclohexyl]₂ZrCl₂ catalyst (ee* = 13%) we have introduced two variations in separate experiments, namely formally exchanged the cyclohexyl for a phenyl group or the methyl for a -CH₂-(9-BBN) substituent, respectively.



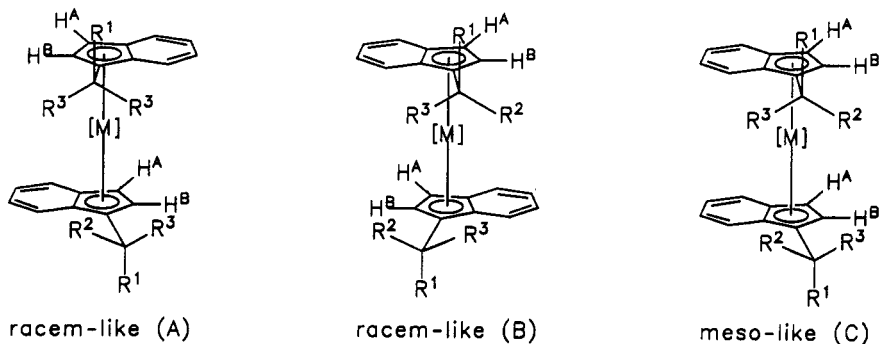
Both variations furnished about the same result with regard to their influence on the polymer stereochemistry: the effectiveness of enantiomorphic site control was about doubled ($[\text{Cp-CH}(\text{CH}_3)\text{phenyl}]_2\text{ZrCl}_2$: $ee^* \approx 25\%$; $[\text{Cp-CH}(\text{CH}_2\text{-9-BBN})\text{cyclohexyl}]_2\text{ZrCl}_2$: $ee^* \approx 30\%$). Both substituent effects combined in a single metallocene catalyst precursor $[\text{Cp-CH}(\text{CH}_2\text{-9-BBN})\text{phenyl}]_2\text{ZrCl}_2$ resulted in a much more effective transfer of the metallocene chirality information ($ee^* \approx 60\%$) in the carbon carbon coupling process. We are hopeful that similar additivity effects will also be applicable to other substituent combinations. This would be very helpful for a future design of stereoselective homogeneous Ziegler catalyst systems.

Another way of introducing persistent metallocene chirality makes use of planar chirality elements. Brintzinger's ansa-bis(indenyl)zirconium halides and the many variations published thereafter are well known and often used examples of this type (ref. 8). A close inspection of the underlying stereochemical principles reveals, however, that the ansa-bridge may not even be a necessary structural element; the analogously substituted bis(1-alkylindenyl)zirconocene halides exhibit the same overall symmetry properties. We have investigated whether such simple non-bridged planarly chiral bis(indenyl)metallocene systems could be used as catalyst components for the stereoselective propene polymerization as well.

using persistent planar chirality



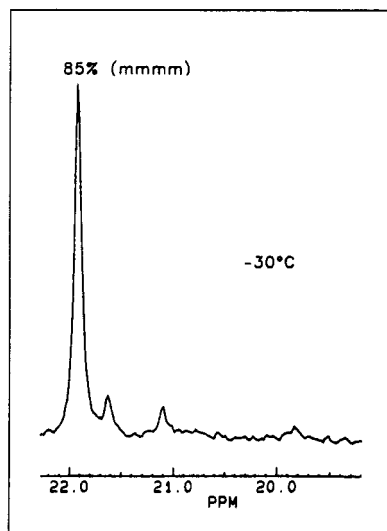
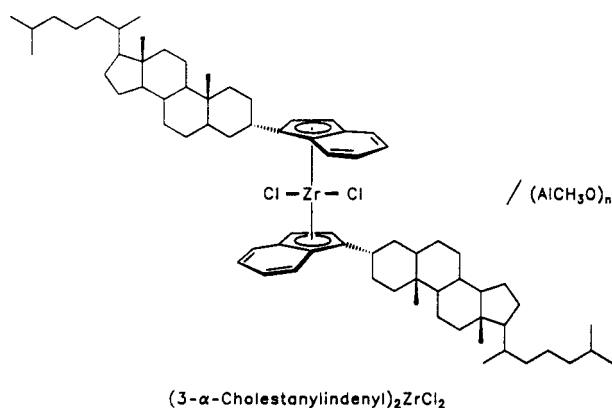
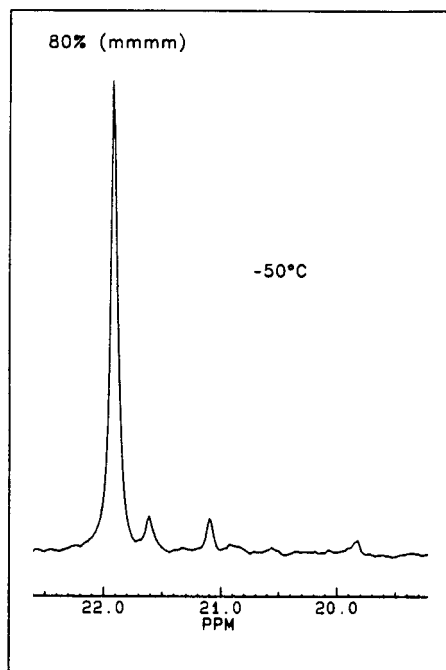
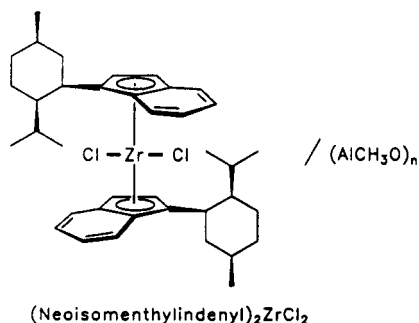
In order to enter into optically active catalyst series directly (which is of importance for a future application of such homogeneous Ziegler systems for the enantioselective catalytic preparation of chiral monomeric organic target molecules) we decided for attaching homochiral side chains to the indenyl ligands originating from the chiral pool. This makes the overall stereochemical situation slightly more complex: instead of just two diastereomers (meso and racem) there are now three separate isomers (two racem-like and one meso-like), all of which are chiral and optically active, provided enantiomerically enriched starting materials were used for their synthesis.



We have prepared a large variety of differently substituted $(R\text{-indenyl})_2\text{ZrCl}_2$ complexes. As a typical example, $(-)$ -menthol was converted to menthyltosylate, then $\text{S}_{\text{N}}2$ -substituted by indenyl lithium. Deprotonation and reaction with 1/2 molar equivalent of zirconium tetrachloride then gave bis(neomenthylindenyl)zirconium dichloride in good yield. The metallocene complex formation in this

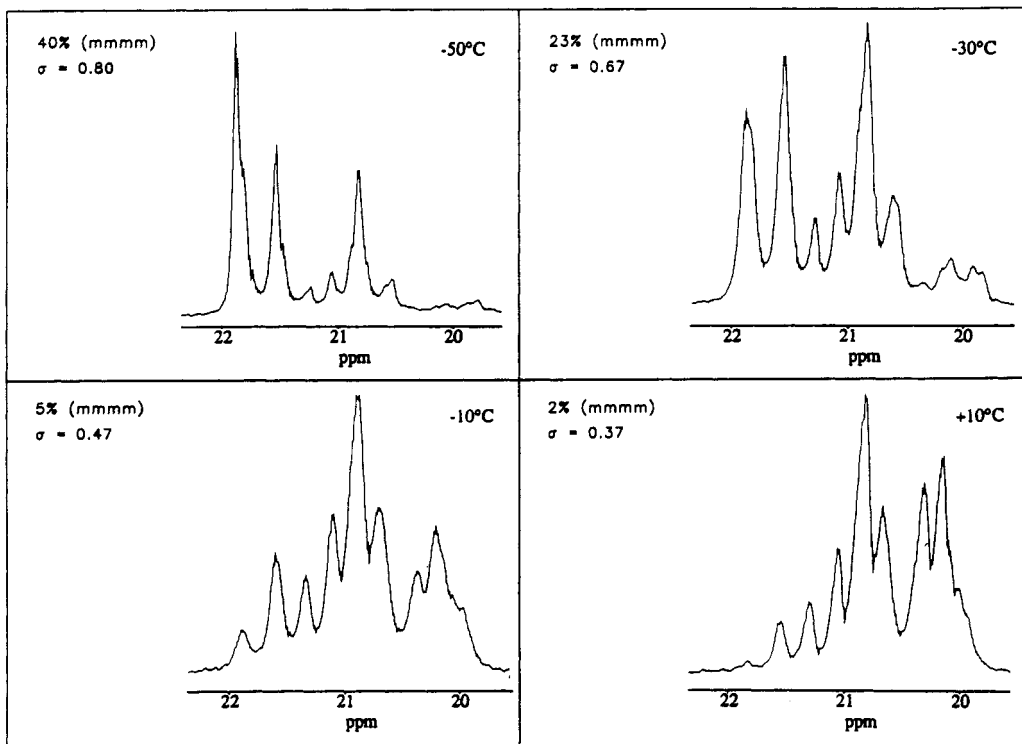
case (as in many others) was rather diastereoselective, leading to the dominating formation (>90%) of one of the racem-like diastereoisomers. Various other substituents (especially originating from terpene or steroid series) were introduced similarly facile.

Diastereomerically (and enantiomerically) pure (R-indenyl)₂ZrCl₂ complexes were activated by treatment with alumoxane to give active catalyst systems for the stereoselective propene polymerization in many cases. In a variety of systems only enantiomorphic site control was observed. Two typical examples are shown below: the racem-like bis(neoisomenthylindenyl)ZrCl₂/(AlMeO)_x catalyst produced isotactic polypropylene exhibiting a ≥80% mmmm ¹³C NMR methyl pentad intensity. The (3-α-cholestanylindenyl)₂ZrCl₂ derived catalyst system was even more effective in transferring the chirality

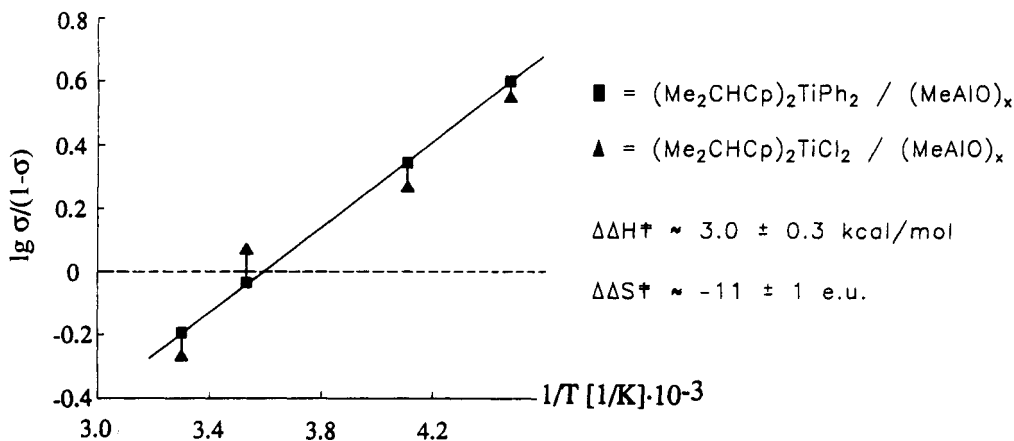


information of the metallocene system on to a growing polymer chain. These examples may suffice to demonstrate that planarly chiral non-bridged bent metallocene complexes may be used for the generation of very stereoselective homogeneous Ziegler catalyst systems as well. They are often much easier prepared with a large structural variability than their ansa-metallocene relatives, and can in a very simple way be obtained optically active avoiding tedious racemate separations. Therefore, such chiral non-bridged bent metallocene complexes may soon become important chiral organometallic auxiliaries and catalyst components, respectively, for carrying out metal complex mediated enantioselective transformations of organic compounds.

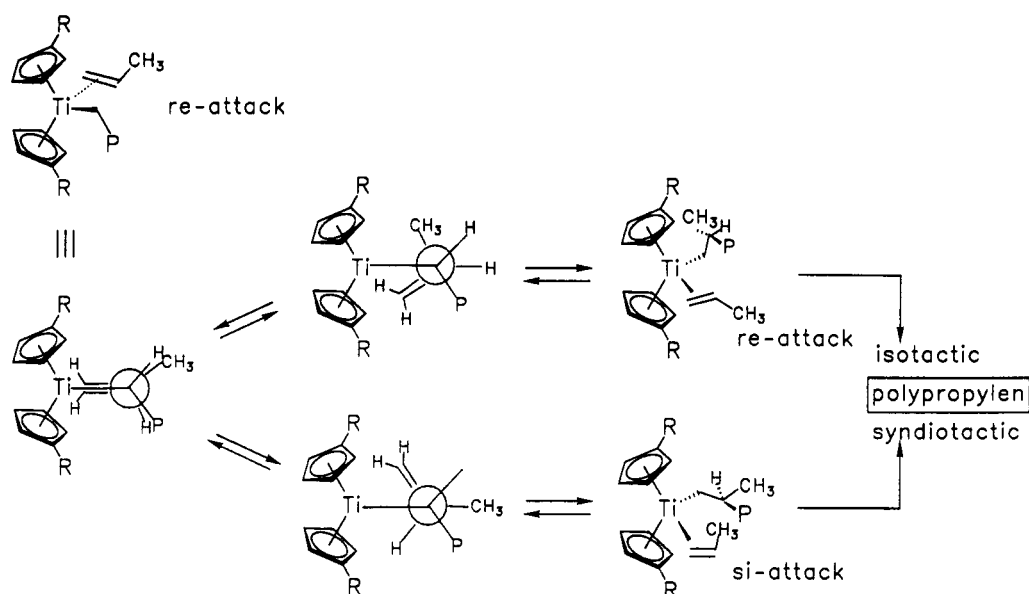
The results described above and many similar observations with the ansa-metallocenes may be tempting to serve as a basis for discussing structure/selectivity relationships at the homogeneous Ziegler catalyst systems, and for enantiomorphic site controlled CC-bond formation that may even be valid. But a word of caution seems to be called for that the situation at such very reactive catalyst systems may sometimes be much more complicated. The following example may serve to illustrate this point. A catalyst system independently prepared by alumoxane activation of bis(isopropyl-Cp)₂titanium dichloride and the corresponding diphenyl derivative gives isotactic block polypropylene at -50°C (chain end control). With increasing temperature, the polymerization process becomes less selective, eventually producing atactic polypropylene at -10°C. Raising the reaction temperature further then results in an overall selectivity increase, the polymer formed at +10°C now is slightly syndiotactic.



An Arrhenius-type plot of the lg of the competition constant $k_{\text{isotactic}}/k_{\text{syndiotactic}}$ (which can be expressed by the numerical value of $\sigma(1-\sigma)^{-1}$ with σ giving the probability to form a m diad) versus T^{-1} gives a straight line in the temperature range looked at. This probably means that isotactic and syndiotactic selectivity control at this bis(isopropylcyclopentadienyl)titanium catalyst system is not completely independent but may just be due to two different branches in a single mechanistic scheme. The two competing reactions very likely have counteracting enthalpic and entropic influence (ref. 13). Under such circumstances the reaction branch with the less negative activation entropy may eventually overtake the enthalpically favoured reaction path and become dominating at high temperature. On the



basis of a widely accepted general mechanism of the propene insertion at such catalyst systems (ref. 14) the following scheme provides a speculative suggestion on how these two competing reaction branches could be described.



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