# Chiral Titanium Complexes for Enantioselective Addition of Nucleophiles to Carbonyl Groups

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## I. Introduction

High selectivity in carbanion chemistry can be obtained, if the counterion, traditionally a main group element, is replaced by a transition metal. Titanium reagents have been applied very successfully in this respect, and the immense progress in this field has been surveyed in a series of general[1] and more specific[2] review articles. The major advantages of titanium and also of zirconium chemistry are the high abundance of these elements, the possibility of adjusting reactivity and selectivity by ligands, and the relative inertness toward redox processes. With the exception of a structurally narrow group of cytotoxic titanocenes[3a-d] and bis-$\beta$-diketonato complexes,[3e-h] titanium and zirconium compounds show no intrinsic biological activity; so far toxic effects can only be related to the ligands. The use of titanium and zirconium as bulk materials, pigments and ceramics, is well established.

After many years of academic endeavor the stereocontrol in organic synthesis has become a major issue for the chemical industry as well.[4] The basic criteria for such applications, economy and ecology, are very well met by titanium reagents. With the importance of carbon–carbon bond formation,[5] especially additions to carbonyls,[6] in mind, this review article is restricted to chiral titanium complexes which transfer a titanium-bound carbon nucleophile to carbonyl groups (Scheme 1). Therefore not included are reactions of achiral titanium complexes with carbonyl groups of chiral substrates and the addition of nucleophiles catalyzed by chiral titanium Lewis acids. (Section III.B might be an exception, since the exact nature of the dialkylzinc/titanium reagents is not known.) Only the most successful titanium reagents are compared with other methods for the same type of transformations.

This article is divided into three main sections, the first describing the synthesis and analysis of chiral titanium complexes. This section is rather general, and it also includes compounds that have not been employed for the transformations described in the subsequent chapters. Many compounds, and among them some of the most efficient reagents, have not been characterized beyond their stoichiometric composition or the symmetry exhibited by their NMR spectra. For clarity, structures are written in brackets if no X-ray determination is published for a specific compound, a precursor, or otherwise closely related complexes (cf. Chart 1, 1 and 2,[7] as examples). In case of dimers and oligomers it has, however, to be kept in mind, that a crystal structure does not necessarily correspond to the structure or an equilibrium of structures in solution.

The chemical transformations with chiral titanium complexes are divided into two chapters, the first dedicated to the addition of $d^1$-nucleophiles (e.g. methyltitanium reagents)[5c,d] and the second to reactions of $d^3$-nucleophiles (e.g. allyltitanium reagents or Ti enolates)[5c,d] with carbonyl compounds. Such a classification accounts for the different mechanism, by which $d^1$- and $d^3$-nucleophiles are added to carbonyl groups (Scheme 2).[6b] For $d^1$-nucleophiles the situation is rather complex, as the four-center transition state **a**,

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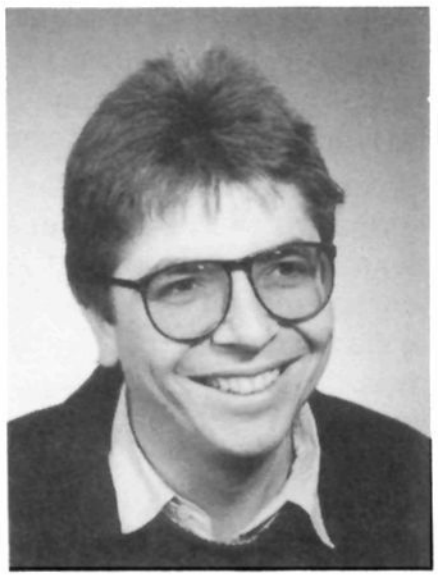
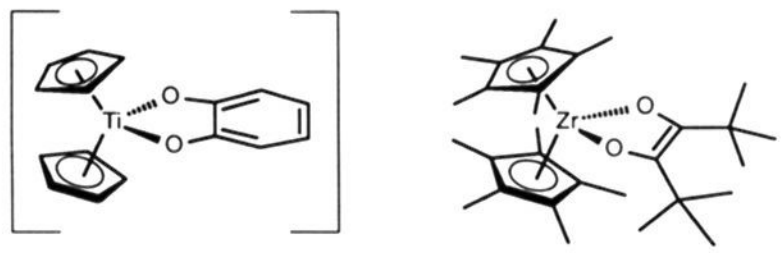
Rudolf O. Duthaler was born in Zürich, Switzerland, in 1946. After graduation at the Eidgenössische Technische Hochschule (ETH), Department of Natural Sciences, in 1969, he did his doctoral studies in organic chemistry with C. Ganter (ETH). His Ph.D. thesis on the photochemical Norrish I cleavage and conformational analysis of hetero-*cis*-decalins was accepted in 1973. He stayed for two more years at the ETH before moving to the United States for a post-doctoral fellowship from John D. Roberts at the California Institute of Technology. After two years of studies in nitrogen(15) NMR he returned to Switzerland in 1977, doing independent research at the ETH in the group of O. Jeger. During this period Duthaler developed an interest in synthetic methodology related to specific problems of natural product synthesis. He joined the Central Research Laboratories of Ciba-Geigy AG, Basel, in 1984. His research topic was first special polymers for electronic materials and later bioorganic chemistry. He took part in the development of novel enantioselective titanium reagents and their application for the synthesis of pheromones, unusual amino acids, and modified carbohydrates. His current research interest is related to synthetic problems in carbohydrate and nucleic acid chemistry. He obtained the Silver Medal of the ETH in 1973 and the award of the Association of Swiss Chemists in 1986. He has been a group leader since 1986 and has been nominated for scientific specialist of Ciba-Geigy in 1989.



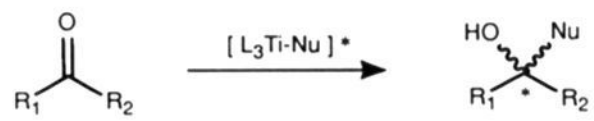
Andreas Hafner was born in Sulgen, Switzerland, in 1956. After graduation at the University of Zürich, Department of Inorganic Chemistry, in 1981 he did his doctoral studies in organic chemistry with W. von Philipsborn (University Zürich). In his Ph.D. thesis, for which he received a "Auszeichnung", he was developing new synthetic methods using iron carbonyl complexes. He was also working in the field of NMR spectroscopy, especially $^{57}Fe$ NMR. Hafner stayed one more year at the University of Zürich before he joined in 1986 the research group of L. S. Hegedus at the Colorado State University. There he did pioneering work in the field of the use of $^{53}Cr$ NMR spectroscopy to elaborate bonding properties and reactivity patterns of chromium carbene complexes in respect to $\beta$-lactam synthesis. In 1988 he joined the Central Research Laboratories of Ciba-Geigy AG and took part in the development of novel enantioselective titanium reagents and their applications for the synthesis of pheromones, unusual amino acids, and modified carbohydrates. His current research interests involve the development of metalloorganic reagents and catalysts for stereoselective and enantioselective synthesis.

**Chart 1**

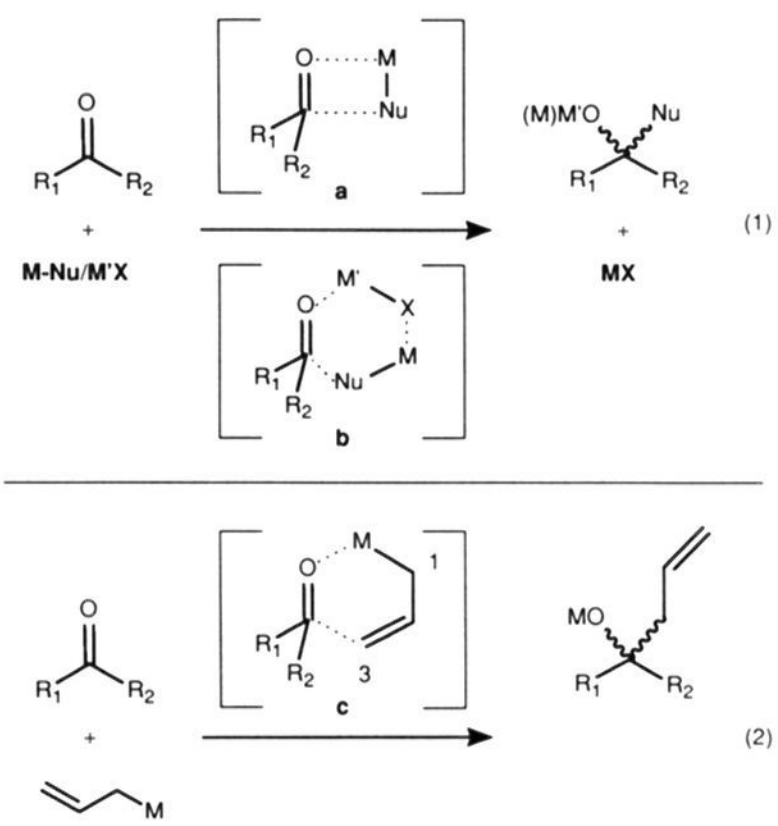



**1** (Ref. 7a) **2** (Ref. 7b)

**Scheme 1**




**Scheme 2**




implied by a bimolecular mechanism, is considered unfavorable in many cases, and a less strained six-center transition state **b** including a third molecule M′–X as mediator has been invoked to explain such processes (Scheme 2, eq 1).[6b,c,d] In ideal cases such a "mediator", which may be a second molecule of the $d^1$-reagent, can be used catalytically. For $d^3$-nucleophiles, on the other hand, a bimolecular six-center cyclic transition state **c** is well established as a mechanistic notion of their 1,2-addition to carbonyls (Scheme 2, eq 2).[8] As the titanium ligands, which are transferred as nucleophiles, are covalently bound, open transition states, proposed for highly ionic reagents,[9] can be neglected. As opposed to primary literature, where scope and limitations of a specific reagent is described, further categorization is done according to reaction types, thus facilitating the comparison of different methods.

## *II. Synthesis and Structures of Chiral Titanium Complexes*

### A. General Remarks

The synthesis of titanium complexes has been extensively reviewed.[1,2] The general principles, by which chiral compounds are obtained as well, are summarized in Scheme 3 (Ti(IV) only). Protic ligands **LH** can

**Scheme 3**

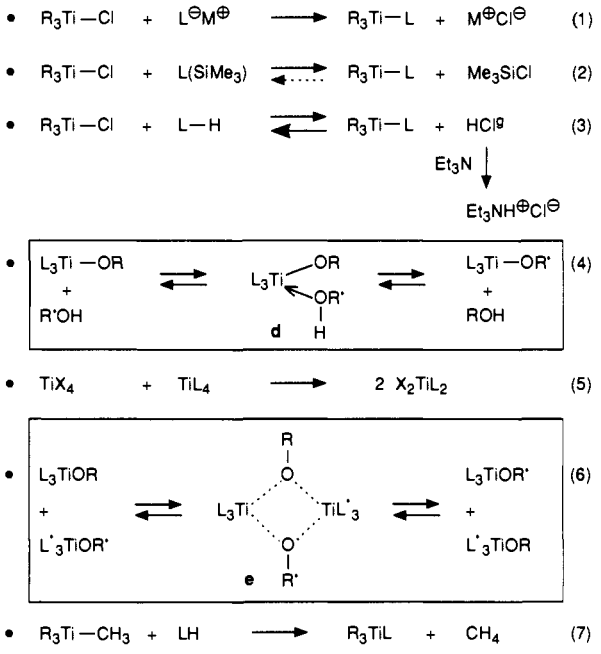
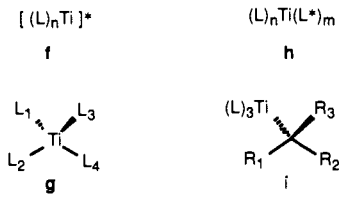


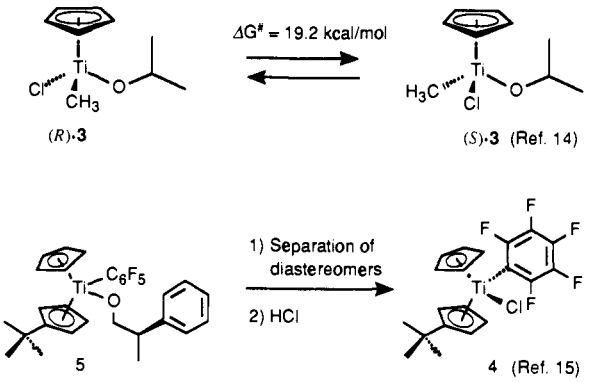
**Chart 2**



substitute a titanium-bound chloride after deprotonation (eq 1), silylation (eq 2), or stannylation. With more acidic ligands $HCl_g$ is evolved spontaneously. The equilibrium, which is usually on the side of the titanium chloride, can be shifted by evaporation of HCl or by neutralization with a weak base (eq 3). A very efficient method for the preparation of titanium alkoxides is the "transesterification" with a free alcohol. The equilibrium is thereby controlled by distillative removal of the more volatile ligand (eq 4). A caveat has, however, to be entered, since these transesterifications never go to completion:[10] variable amounts of alcohol are retained via adduct **d**.[11] This has to be kept in mind, if such mixtures are used for further transformations without purification. Very interesting is the observation, that molecular sieves can affect such equilibria quite substantially.[10a,b] In certain cases (X = halide; L = OR or cyclopentadienyl) ligand redistribution reactions result in comproportionation as shown by eq 5.[12] Alkoxide ligands can be interchanged without the need of free ROH via bridged dimers **e** (eq 6). Such polynuclear aggregates are often the favored form of such complexes, even in solution.[13] Furthermore, the equilibria of eqs 2–6 are very much dependent on electronic and steric factors as well. Finally, a very mild method to introduce protic ligands is displacement of an alkyl ligand from titanium (eq 7).

For the following discussion the chiral titanium complexes are grouped according to different structural types as shown in Chart 2. The chirality of complexes **f** with achiral ligands is based solely on the geometrical arrangement, a special case being a tetrahedrally coordinated titanium with four different ligands (stereogenic Ti, **g**). In the most common case h the asymmetry is due to chiral ligands. The bond to titanium can be involved in the chirality of such ligands as shown by structure i. While the synthesis of structures **h** is straightforward, stereoselective transformations or separation of stereoisomers is needed for the preparation of **f**, **g**, and i. Furthermore, any combination of two of the principles shown in Chart 2 allows the formation of diastereomeric mixtures.

**Scheme 4**



## B. Chiral Titanium Complexes from Achiral Precursors

### *1. Chiral Complexes with Tetrahedral Geometry*

Titanium(IV) compounds with four different ligands are chiral, titanium being a stereogenic center. Reetz and co-workers could demonstrate by NMR that coordinatively unsaturated compounds like complex **3** with only one cyclopentadienyl ligand undergo fast racemization (Scheme 4).[14] Titanocenes are, however, configurationally stable, and compound **4** with two differently substituted Cp ligands can be resolved.[15] Thus, after the introduction of a chiral alkoxy ligand, the resulting diastereomers **5** can be separated chromatographically. The chiral auxiliary can then be replaced stereoselectively by halide.[16] Unfortunately other transformations, e.g. the transmetalation of allylmagnesium chloride with **4** are less stereoselective.[14]

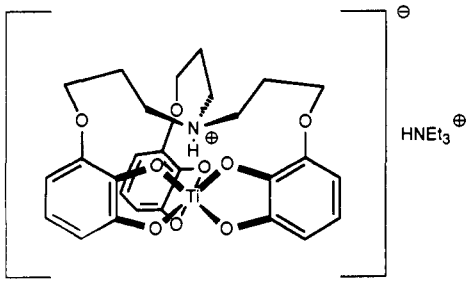
### *2. Chiral Complexes with Octahedral Coordination Geometry*

Octahedral complexes with three identical bidentate ligands are chiral. The bis-cinchoninium salt of triscatecholato titanate has been separated in its diastereomers by crystallization. Due to fast racemization the resolving agent could not be separated from the optically active titanate.[17] Since then the octahedral coordination geometry of such catecholates has been verified by crystal structure analysis.[18] An interesting example is the bridged complex **6** shown in Chart 3.[18b] Such chiral octahedral titanium complexes should principally be accessible using other bidentate ligands as well. Due to the facile racemization and the coordinative saturation, such structures are, however, unsuited for chemical transformations.

### *3. Titanium Complexes with Planar Chirality*

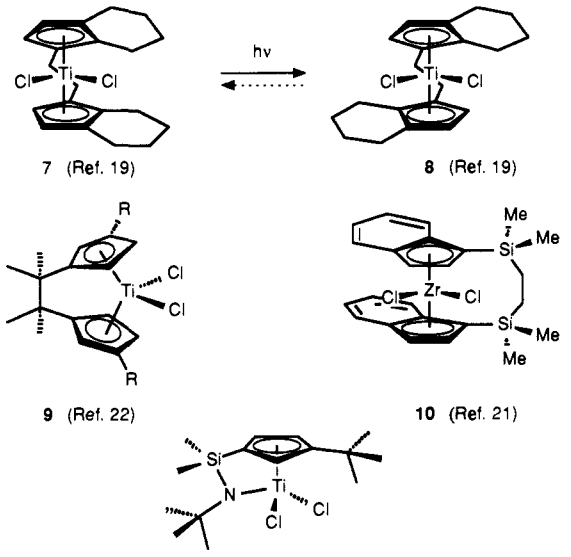
Titanocenes with two or more different substituents on their cyclopentadienyl ligands can represent "planar chirality". The classical bis(tetrahydroindenyl)ethane

**Chart 3**



6 (Ref. 18b)

**Chart 4**

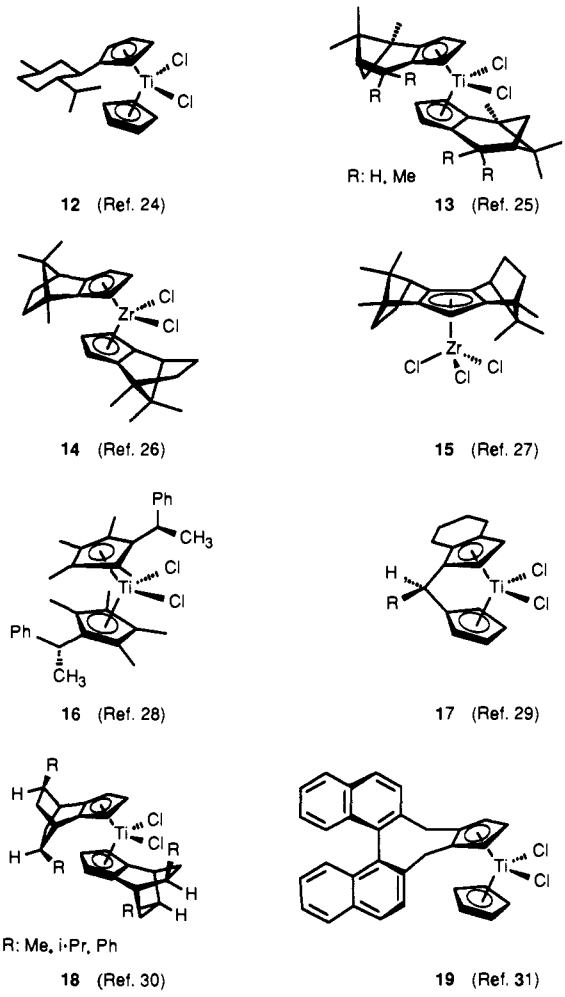


7 (Ref. 19) 8 (Ref. 19)

9 (Ref. 22) 10 (Ref. 21)

11 (Ref. 23)

**Chart 5**



12 (Ref. 24) 13 (Ref. 25)

14 (Ref. 26) 15 (Ref. 27)

16 (Ref. 28) 17 (Ref. 29)

18 (Ref. 30) 19 (Ref. 31)

ligand introduced by Brintzinger and co-workers[19] affords the meso compound **7** and its chiral isomer **8** (Chart 4). The diastereomers can be equilibrated photochemically and racemic **8** can be resolved via its 1,1'-binaphthyloxy derivative. These systems have been studied extensively, mainly because cationic complexes derived from **8** or its zirconium analog are catalysts for stereoregular olefin polymerization.[20,21] Variations of this system include differently substituted cyclopentadienyl ligands (e.g. **9**[22a-c]) and similar compounds.[22d] The distortion exerted by the longer ansa chain of **10** has interesting effects on the catalyst activity and selectivity.[21] Closely related to these titanocenes is the monocyclopentadienyltitanium complex **11** with a chelating amino ligand attached to the cyclopentadienyl ring, described recently by Okuda.[23]

## C. Titanium Complexes with Chiral Ligands

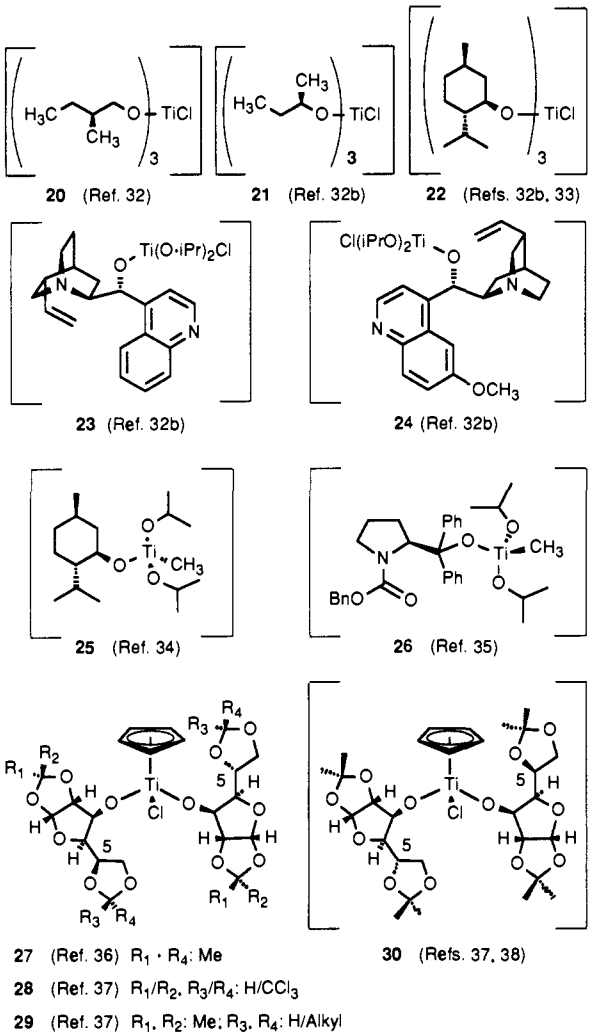
### *1. Cyclopentadienyl Ligands with Chiral Substituents*

Due to their stability $\eta^5$-bound Cp ligands are well suited for chiral modification of titanium complexes. If the chirality is derived from natural products, the separation of enantiomers can be avoided. Menthylcyclopentadiene used for the preparation of titanocene **12**[24] was one of the first representatives (Chart 5). To gain rigidity, Paquette and co-workers prepared cyclopentadienes fused to pinene and bornane skeletons. As these ligands lack symmetry, diastereomers are formed. In addition to the favored endo,endo isomers **13**[25] and **14**[26] shown in Chart 5, the exo,exo and endo,-exo diastereomers are also obtained. This problem is avoided in the case of the zirconium complex **15**,[27] because the ligand fused to two camphanes has $C_2$ symmetry. Chirally modified cyclopentadienes not derived from natural products have been used as ligands for the titanium complexes **16**,[28] **17**,[29a,b] **18**,[30] and **19**[31] (Chart 5). Interestingly, only one of two possible diastereomers is formed in the case of **17** and related compounds.[29] Such ambiguity is not possible for **18** and **19**, as their ligands have $C_2$ symmetry.

### *2. Titanium Complexes with Chiral Monodentate Ligands*

Optically active alcohols are the favored monodentate ligands for the preparation of chiral titanium reagents. Most convenient is again the use of natural products or derivatives thereof. Thus, the monochloro titanates **20**,[32] **21**,[32b] **22**,[32b,33] **23**,[32b] and **24**[32b] (Chart 6) were prepared by transesterification of $ClTi(O\text{-}i\text{-}Pr)_3$ with 1 or 3 equiv of a chiral alcohol according to eq **4** of Scheme 3. The methyltitanium compounds **25**[34] and **26**,[35] on the other hand, were obtained by methyl displacement from $Me_2Ti(O\text{-}i\text{-}Pr)_2$ (eq 7, Scheme 3). The compounds **20–26** have been used for further reactions without purification and characterization. An equilibrium of different polynuclear species and fast ligand exchange can be assumed for their solutions. This tendency can be suppressed by the electronic and steric influence of cyclopentadienyl ligands. Conse-

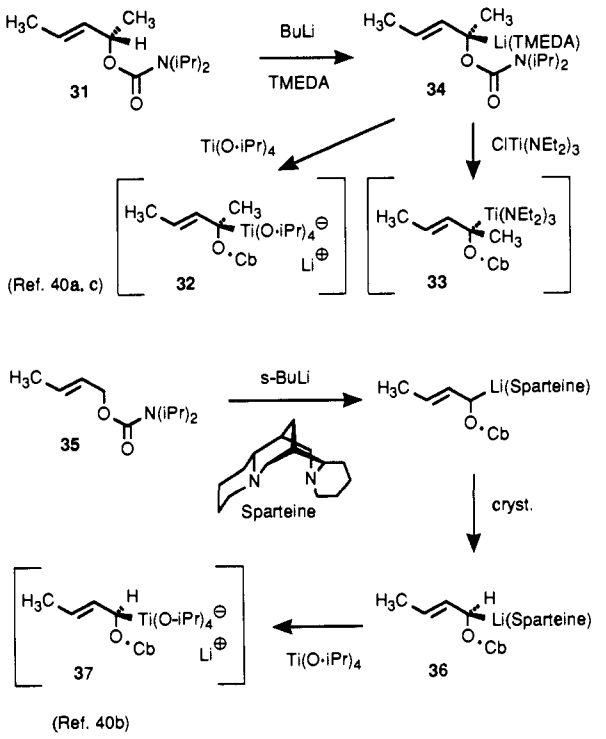
**Chart 6**




quently, complex **27**, obtained from $CpTiCl_3$ and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose according to eq 3 (Scheme 3), is monomeric and its structure could be confirmed by $^1H$ and $^{13}C$ NMR, as well as by X-ray diffraction.[36b] Structures with comparable properties could be obtained by using different acetal protection for the D-glucose derived ligands (e.g. **28** and **29**[37]). The complexes **27–29** show two sets of $^1H$ and $^{13}C$ NMR signals for the diastereotopic alkoxy groups; an indication that ligand exchange, if occurring at all, is slow. Unfortunately, this is not a general feature of dialkoxycyclopentadienyltitanium chlorides, and even seemingly minor changes of the sugar skeleton leads to extremely labile compounds. Complex **30**, obtained from 1,2:5,6-di-*O*-isopropylidene-α-L-idofuranose (the C(5)-epimer of glucose) could not be analyzed by NMR, as only the signals of free ligand were observed, no matter what precautions were taken to exclude moisture.[37,38] Similar observations were made with ligands derived from D-xylose or D-allose.[39a]

While the chiral ligands of the complexes shown in Chart 6 remain bound to titanium, chirality of the reacting nucleophilic ligand is another effective approach to stereoselective carbonyl additions. If titanium is attached to a chiral C atom, stereoselective transformations are needed for the preparation of such reagents. This route has been pursued successfully by Hoppe and co-workers (Scheme 5).[40] The chiral carbamate **31** can be lithiated with retention of configuration, and depending on the method of transmetalation, titanium can be introduced either with retention (**32**) or inversion (**33**).[40a] Alternatively, the organolithium reagent **34** can be obtained from racemic **31** by enantiomer differentiating deprotonation with *sec*-butyllithium–sparteine.[40c] If the achiral carbamate **35** is lithiated with *sec*-butyllithium–sparteine, the chiral organolithium compound **36** is obtained in high optical purity by crystallization of the equilibrating racemate. Titanation without loss of optical activity is possible (**37**).[40b] The structure of a organolithium compound related to **36** has been elucidated by X-ray analysis.[41]

**Scheme 5**




Closely related to the stereoselective metalation of allylic carbamates is the preparation of the titanium reagent **38** from the *N*-allyl urea **39** (Scheme 6).[42] In this case a chiral auxiliary directs the diastereoselective titanation via deprotonation with *n*-BuLi and transmetalation.

**Scheme 6**

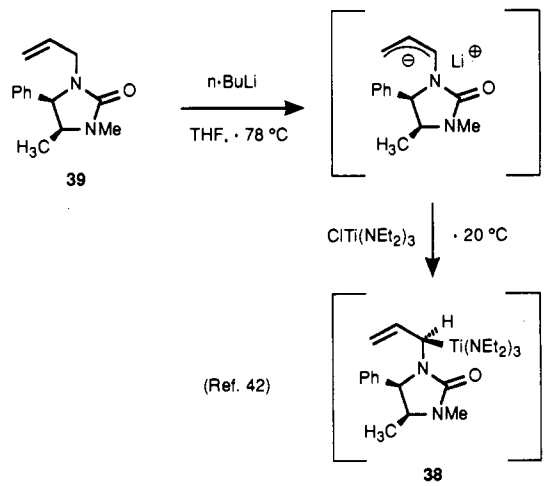
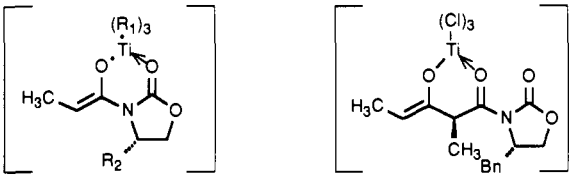


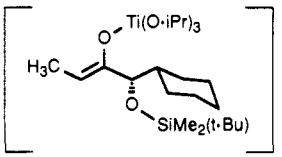
**Chart 7**



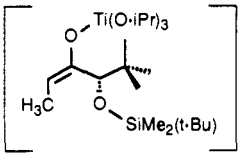
**40** $R_1$: O-iPr $R_2$: i-Pr (Ref. 43)
**44** $R_1$: Cl $R_2$: Bn (Ref. 47)



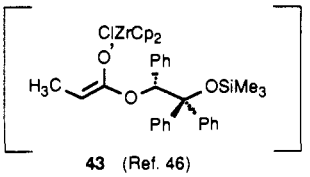
**45** (Ref. 48)



**41** (Ref. 44)



**42** (Ref. 45)



**43** (Ref. 46)

Covalently bound chiral auxiliaries or asymmetric centers, which do not participate in reactions, are necessary for the design of chiral enolate ligands. The titanium enolates depicted in Chart 7 have been recently developed as highly stereoselective propionyl nucleophiles. The triisopropoxytitanates **40**,[43] **41**,[44] and **42**,[45] as well as the zirconocene derivative **43**,[46] were obtained by transmetalation of the corresponding Li enolates with $ClTi(O\text{-}i\text{-}Pr)_3$ or $Cp_2ZrCl_2$ according to eq 1 (Scheme 3). When $TiCl_4$ is used, the enolization, exemplified by **44**[47] and **45**,[48] can be effected by diisopropylethylamine (cf. eq 3, Scheme 3).[47-49]

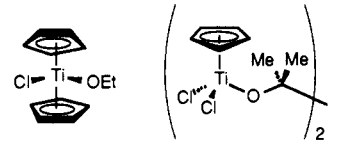
### 3. Titanium Complexes with Chiral Bidentate Ligands

The idea of using bidentate chiral ligands originates from the expectations that the chelate rings stabilize such complexes and that the rigidity gained should improve the stereoselectivity of the corresponding reagents. Since the methods for the preparation of such structures are based on thermodynamically controlled equilibria (cf. Scheme 3), the stabilities of the target complexes should be carefully evaluated. In addition to entropic factors, the crucial parameters for ring formation are the Ti–X–C and X–Ti–Y bond angles, as well as the Ti–X bond lengths. These values not only depend on the atoms X and Y but to a very large extent also on the number of $\eta^5$-bond Cp ligands. Table 1 lists such data, obtained by crystal-structure analysis of titanocenes **46**,[50a] **46a**,[50c] and **46b**[50d] and of the monocyclopentadienyltitanates **27**,[36b] **47**,[50a] **48**,[39a] and **49**[39a] (Chart 8). The Ti–O bond lengths, estimated 210 pm for a "single bond",[50a] are considerably shorter (175–197 pm), thus indicating additional bonding by $\pi$-donation of the oxygen lone pairs. This is also reflected by the obtuse Ti–O–C bond angles of 133° to 166°. This effect correlates with the Lewis acidity of titanium, which is mainly governed by the number of Cp ligands. A similar tendency is observed for the X–Ti–Y bond angle with 93° for the titanocene **46** and 98–104° for the mono-Cp complexes. As shown by the examples

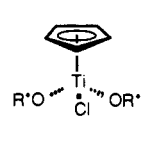
**Table 1. Selected Structural Parameters of Cyclopentadienyltitanium Complexes**[36b,39,50a,c,d]

| compd | Ti–O bond length, pm | Ti–O–C bond angle, deg | X–Ti–O bond angle, deg |
|---|---|---|---|
| **46** | 186 | 133 | 93 (X = Cl) |
| **47** | 175 | 166 | 102 (X = Cl) |
| **27** | 181 | 146 | 104 (X = O) |
| | 179 | 153 | |
| **48** | 176 | 149 | 98 (X = O) |
| | 178 | 148 | |
| **49** | 179 | 145 | 98 (X = O) |
| | 178 | 155 | |
| **46a** | 190 | 146 | 95 (X = O) |
| **46b** | 197 | 143 | 90 (X = O) |
| | | 149 | |

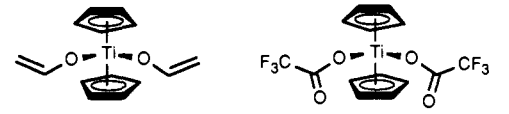
**Chart 8**



**46** (Ref. 50a) **47** (Ref. 50a)



**27** (Chart 6, Refs. 36b, 39a)
**48** (Scheme 10, Ref. 39a)
**49** (Scheme 10, Ref. 39a)



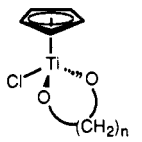
**46a** (Ref. 50c) **46b** (Ref. 50d)

**46a**[50c] and **46b**,[50d] the nature of the oxygen ligand has a substantial influence on these parameters. The Ti–O bond length of an enolate (**46a**) or an acyl group (**46b**) is bigger (190 pm and 197 pm, respectively), and yet the Ti–O–C bond angles (143–149°) are widened considerably, when compared with **46**. These angles are most probably influenced by the $sp_2$ hybridization of C($\alpha$) through delocalization of the oxygen lone pair into the carbon $\pi$-system. Such effects have therefore to be considered for acyl and phenolic ligands (e.g. Chart 11).

From the data of Table 1 it is evident, that dialkoxy ligands forming small rings should give rise to considerable strain and therefore unstable complexes. The relative strain energies of the model structure **j** have been estimated by force field calculations (MACROMODEL, version 2.5), using the geometrical parameters of **27**, determined by X-ray diffraction,[36b,39a] and charge parameters resulting from an ab initio calculation of cyclopentadienyldimethoxytitanium chloride.[51] The results, shown in Table 2, clearly demonstrate, that five- and six-membered rings are strained, while larger rings match the geometrical parameters of Table 1. According to these calculations the seven-membered ring ($n$ = 4) is optimal.

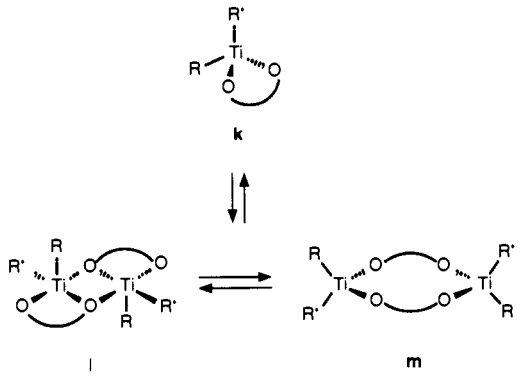
Following the general trend, the Lewis acidity of alkyl and aryl titanates lacking cyclopentadienyl ligands is enhanced to such an extent that, in the absence of other ligands, the coordinative unsaturation is overcome by the formation of aggregates (Scheme 7).[13b,d] The strain of cyclic monomers **k** is thereby reduced,[52] and even five-membered rings can be incorporated in dimers or higher oligomers of type **l**. A further complication is

**Table 2. Relative Ring-Strain Energies of Titanacycles j, Calculated with MACROMODEL (Version 2.5)[51]**



| n | energy, kJ/mol | Ti-O-C bond angle, deg | O-Ti-O bond angle, deg |
|---|---|---|---|
| 2 | +27.2 | 126 | 79 |
| 3 | -22.5 | 137 | 89 |
| 4 | -30.6 | 147 | 96 |
| 5 | -20.4 | 148 | 99 |
| 6 | -10.6 | 150 | 98 |

**Scheme 7**



k

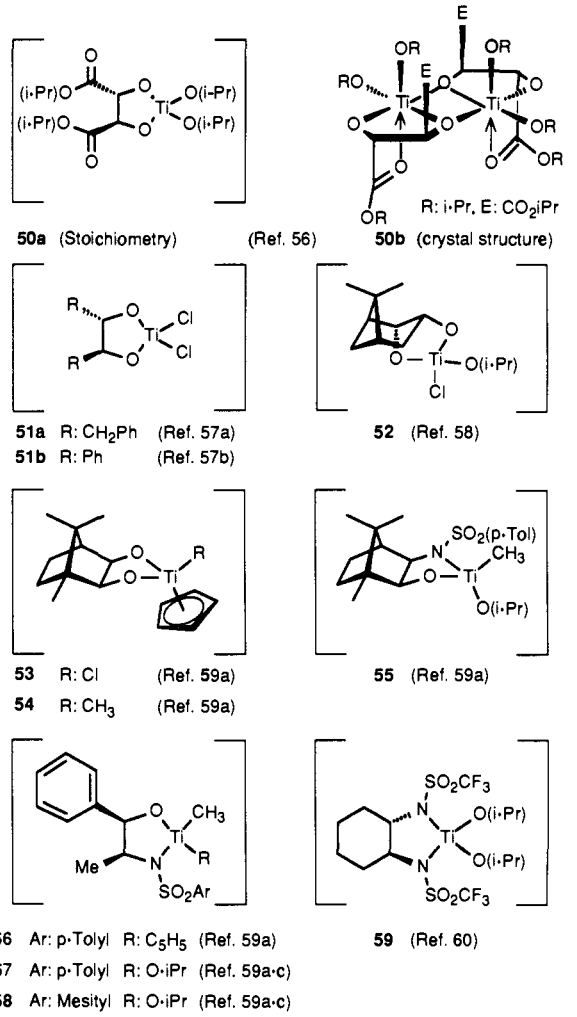
l m

the equilibrium between the tricyclic species **l** and the macrocycle **m**, which is influenced by subtle structural differences.[53]

Several monomeric five-membered titana- and zirconacycles have been confirmed by crystal structure analysis.[7b,54] These complexes are, however, obtained by different methods than those listed in Scheme 3, e.g. by intramolecular bond formation of reactive ligands. Furthermore, bulky groups, like the Cp* ligands of **2** (Chart 1),[7b] provide kinetic stabilization against the formation of thermodynamically favored compounds via ligand exchange (eq 6, Scheme 3). It has to be noted, that nitrogen or sulfur ligands are often used for such structures.[54] Since the Ti-N(S) bond energy is lower than the energy of Ti-O bonds,[55] the Ti-N(S)-C bond angle is also less obtuse, thus reducing the ring strain of such titanacycles. A recent example is the bis-titanocene complex of the benzene-1,2,4,5-tetrathiolato ligand.[54f]

Titanium complexes obtained from chiral 1,2-diols or the corresponding sulfonamides are therefore with certainty not the monomers shown in Chart 9. The most famous example is the Sharpless catalyst **50**. It could be proven by several crystal-structure analyses and NMR studies[53,56] that the strained $(i\text{-PrO})_2$Ti/tartrate monomer **50a** is stabilized by dimerization to **50b** or similar aggregates. Complexation of one ester carbonyl per titanium affords thereby an octahedral coordination. The other structures of Chart 9 (**51**–**59**[57–60]) are most probably such aggregates as well. With the exception of **53** and **54**, which are homogeneous according to $^1$H and $^{13}$C NMR,[59a] mixtures of varying composition can be assumed for the other preparations. Good evidence, based on NMR arguments, for an oxo-bridged dimer **l** (Scheme 7) has recently been reported

**Chart 9**



**50a** (Stoichiometry) (Ref. 56)

**50b** (crystal structure) R: i-Pr, E: $CO_2$iPr

**51a** R: $CH_2Ph$ (Ref. 57a)
**51b** R: Ph (Ref. 57b)

**52** (Ref. 58)

**53** R: Cl (Ref. 59a)
**54** R: $CH_3$ (Ref. 59a)

**55** (Ref. 59a)

**56** Ar: p-Tolyl R: $C_5H_5$ (Ref. 59a)
**57** Ar: p-Tolyl R: O-iPr (Ref. 59a-c)
**58** Ar: Mesityl R: O-iPr (Ref. 59a-c)

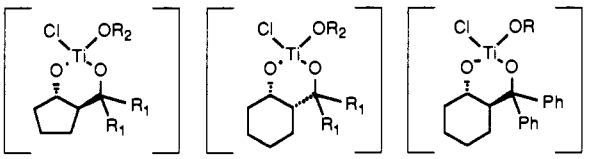
**59** (Ref. 60)

for the dichloro analog of **53**/**54**.[13d] Reetz and Kükenhöhner could demonstrate that the method of preparation is crucial and that the reagents **55**–**58** are best prepared from $TiMe_4$ and $CpTiMe_3$, respectively, according to eq 7 of Scheme 3.[59] *N*-Sulfonylephedrines with substituted aromatic rings have recently been prepared from alanine.[59d] Their use as titanium ligands allows efficient kinetic resolution of 2,3-epoxy alcohols.[59d]

The ring strain of six-membered titanacycles derived from 1,3-diols should be reduced, when compared to the corresponding chelates of 1,2-diols (cf. Table 2). Structural data, however, show that such complexes form alkoxo-bridged dimers as well,[52] or else ring formation could not be observed.[50b] Cyclization is also hampered by entropic effects due to the greater conformational freedom of 1,3-diols. Diols with restrained flexibility have therefore been chosen as ligands for the complexes **60**–**62** (Chart 10).

According to the strain-energy estimation shown in Table 2, 1,4-diols leading to seven-membered rings are the optimal ligands for chelated titanium complexes. 1,1'-Binaphthol is a rigid chiral 1,4-diol, which fulfills these expectations by formation of monomeric cyclic complexes with titanocenes,[19a,22b,61] e.g. **63**[61] (Chart 11). The structure of the 1,1'-binaphthyloxy derivative of the *ansa*-titanocene **8** (Chart 4) has been determined by X-ray diffraction.[19a] However, the bond angles, 122–123° for Ti-O-C and 94° for O-Ti-O, clearly imply that the preferred geometry of this ligand is less suited

**Chart 10**



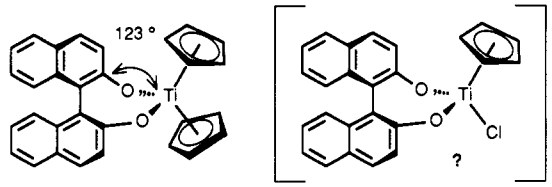
60 $R_1$: Me, Ph; $R_2$: i-Pr, Ph

61 a $R_1$: Ph, $R_2$: i-Pr; b $R_1$: Me, $R_2$: Ph

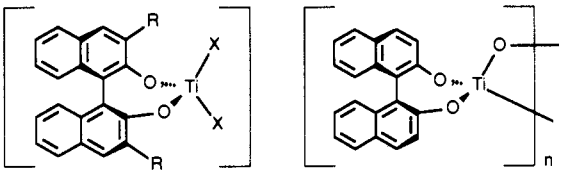
62

(Ref. 58)

**Chart 11**



63 (Ref. 61) 64 (Ref. 61)



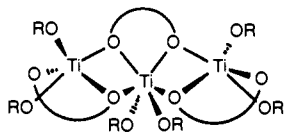
65 R: H X: Cl (Ref. 65)

66 R: H X: O-iPr (Refs. 64, 66)

67 R: H X: Cl, O-iPr (Refs. 32b, 66)

68 R: Ph X: Cl (Ref. 67)

69 (Ref. 69)

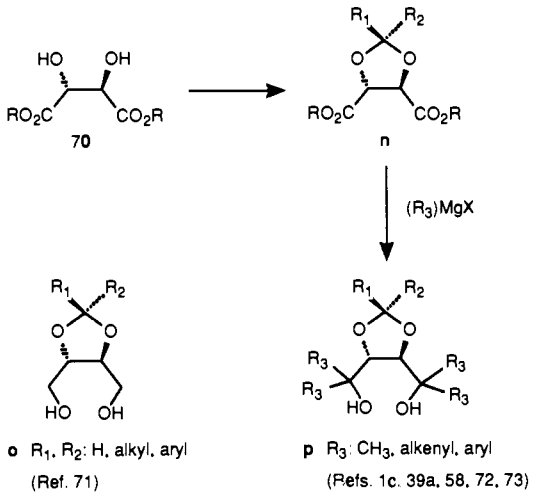


66 (Crystal structure, ref. 64, schematic representation)

for monocyclopentadienyltitanates, requiring 145–166° for the Ti–O–C and 98–104° for the O–Ti–O bond angles (cf. Table 1). It is therefore not astonishing that complex **64** could not be prepared from $CpTiCl_3$ either by method 1 or 3 (Scheme 3).[61,62a] No structural proof is given in a recent paper claiming the preparation of **64** and similar compounds.[62b] Oxidative chlorination of the Ti(III) analog might afford **64**, but the $^{13}C$ NMR reported in ref 61 is not conclusive, as the shift values correspond to the signals of free ligand.[63] The complexes **65–68**[32b,64–67] obtained from precursors lacking Cp ligands are again stabilized by aggregation, and the crystal structure of **66**, the trimer shown schematically in Chart 11, could be solved by X-ray diffraction.[64] Aggregate formation is also made responsible for the nonlinear correlation of optical purity and enantioselectivity of reagent **65**.[65b] The oxide **69**, obtained from partially hydrolized $(i\text{-PrO})_4Ti$,[68a] is an interesting Lewis acid catalyst.[69] Its structure might be rather complex, as the precursor has recently been shown to be a complicated mixture of oligomers, containing, among others, $[Ti_7O_4](OR)_{20}$ and $[Ti_8O_6](OR)_{20}$ clusters.[68b,c] Finally, in the patent literature a (1,1'-binaphtholti-tanium(IV) complex of 2:1 stoichiometry is claimed.[70]

A whole array of chiral 1,4-diols, suited for the preparation of titanium chelates, can be prepared from

**Scheme 8**

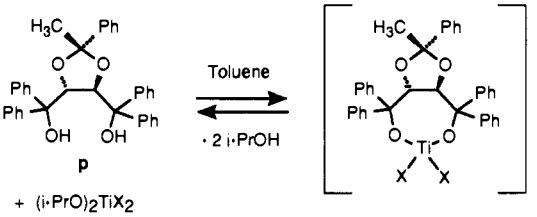


70 n

o $R_1$, $R_2$: H, alkyl, aryl (Ref. 71)

p $R_3$: $CH_3$, alkenyl, aryl (Refs. 1c, 39a, 58, 72, 73)

**Scheme 9**



p + $(i\text{-PrO})_2TiX_2$

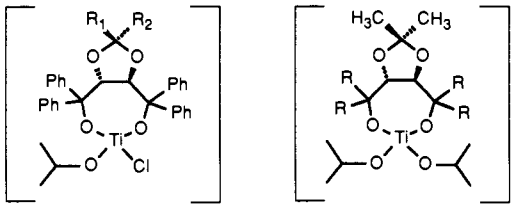
| | | | | |
|---|---|---|---|---|
| 13 | : | 87 | 71 X: Cl | (Ref. 10a) |
| 6 | : | 94 | (mol sieves) | |
| 25 | : | 75 | 72 X: i-PrO | (Ref. 10b) |

(*R*,*R*)- or (*S*,*S*)-tartrates **70** by acetalization (**n**) followed by hydride reduction or addition of Grignard reagents (**p**, Scheme 8).[1c,39,58,71,72] The conversion of **n** to **p** is, however, restricted to methyl, vinyl, and aryl Grignard reagents. Problems are encountered with organolithium compounds,[58] and reduction rather than addition occurs with Grignard reagents having H-substituted saturated β-carbons.

While polymeric titanium complexes are formed with ligand **o** ($R_1$, $R_2$ = $CH_3$),[2a,39a] spontaneous chelation occurs with the diols **p** ($R_3 \neq H$) and titanium alkoxides. The Ingold/Thorpe effect[74] is obviously responsible for an ideal "chelation conformation". By $^1H$ NMR Narasaka could show that the equilibrium is 87:13 in favor of complex **71** and 75:25 in the case of **72** (Scheme 9).[10] Addition of molecular sieves shifted the equilibrium position to 94:6 for **71**.[10a] Further complexes, obtained either from $(i\text{-PrO})_3TiCl$ (**73–75**)[58] or from $(i\text{-PrO})_4Ti$ (**76–78**),[75,76] are listed in Chart 12. The structure of the spirocyclic titanate **78** could be determined by X-ray diffraction.[76] If **78** is mixed with 1 equiv of $(i\text{-PrO})_4Ti$ a comproportionation according to eq 5 of Scheme 3 affords two monocyclic complexes **76**.[76] At present it is not clear whether the complexes **71–77** are monomeric structures or aggregates. Single resonances in the NMR spectra point to monomers or highly symmetrical dimers. However, the observation reported by Narasaka,[10a] that an insoluble precipitate is formed with racemic ligand, is a clear indication of aggregation, at least for racemates.

The stable cyclopentadienyl- and 1,2,3,4,5-pentamethylcyclopentadienylchlorotitanates **48**, **49**, **79**, **80**, and further seven analogs not shown in Scheme 10 have been obtained from ligands **p** according to eq 3 of

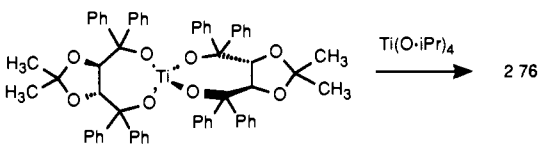
**Chart 12**



73 $R_1$, $R_2$: $CH_3$ (Ref. 58)
74 $R_1$: H, $R_2$: mesityl (Ref. 58)
75 $R_1$: H, $R_2$: t-Bu (Ref. 58)

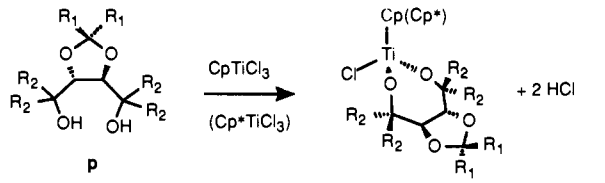


76 R: Ph (Refs. 75a, c)
77 R: 2-Naphthyl (Ref. 75c)



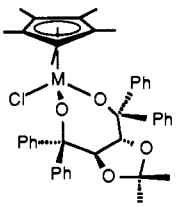

78 (Refs. 75b, 76)

**Scheme 10**




p

48 $R_1$, $R_2$: $CH_3$ Cp (Ref. 39a)
49 $R_1$: $CH_3$, $R_2$: Ph Cp (Refs., 38, 39a)
79 $R_1$: H, $R_2$: Ph Cp (Ref. 39a)
80 $R_1$, $R_2$: $CH_3$ Cp* (Ref. 39a)

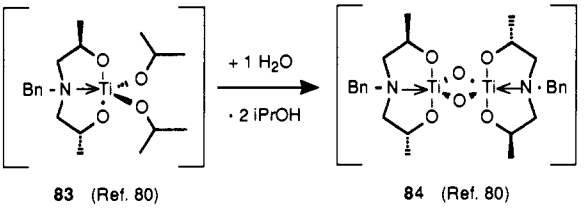


81 M: Zr (Refs. 38b, 78)
82 M: Hf (Refs. 38b, 78)

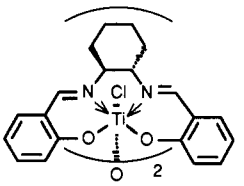
Scheme 3.[38,39a] The $HCl_g$ evolving spontaneously is either neutralized at RT with $Et_3N$ in $Et_2O$ or removed in a stream of argon at 80–100 °C in toluene or cyclohexane. The resulting solutions can be used in situ for further reactions, or else the crystalline complexes can be precipitated with hexane and purified further by crystallization. In this way complex **49** is routinely prepared in 1-kg batches.[39b] The structures of **48**,[39a] **49**,[39a] and **79**[77] have been confirmed by X-ray diffraction. The geometrical parameters of **48**, **49**, and also **79** match well with those of the acyclic analog **27** (cf. Table 1), thus indicating the absence of ring strain for such seven-membered titanacycles. In addition to these titanium chelates, the analogous 1,2,3,4,5-pentamethylcyclopentadienylzirconium and -hafnium complexes **81** and **82** have been prepared using either method 1 or 3 of Scheme 3 (Scheme 10).[38b,78]

Titanium chelates with larger than seven-membered rings should be comparatively unstrained, according to the estimated parameters listed in Table 2. Their formation might, however, be hampered by entropic effects. The crystal structures of a few achiral eight-membered titanacycles have been reported.[79] Formally larger rings can be obtained, if additional heteroatoms, capable of coordination, are incorporated, thereby affording multidentate ligands. Interesting examples of such ligands, leading to chiral complexes, are shown in Chart 13. The ligand of the appealing bicyclic structure **83** is conveniently obtained from optically active propylene oxide and benzylamine.[80] Partial hydrolysis of **83** affords an oxide which must have a polynuclear structure, since, with extremely rare exceptions, terminal oxo complexes of titanium and zirconium are unknown.[81] The dimer **84** is a reasonable proposal for the structure of this oxide, as several X-ray determinations of such oxides have been reported,[18a,82] the closest analog being compound **85**.[82c] While the structure of the μ-oxo dimer **86**, derived from a chiral salen ligand has been secured by X-ray analysis,[83] many possibilities can be envisaged for the complex **87**, which is prepared from the 1-formyl-2-naphthol imine derivative of H-Val-Trp-$OCH_3$ and $(EtO)_4Ti$.[84a] Related is the complex **88**, prepared recently using the Schiff's base of 3-*tert*-butylsalicyl aldehyde and valinol as Ti ligand.[84b] Chiral titanium chelates with coordinating ligands include the sparteine complex of $MeTiCl_3$ reported by Reetz[85] and the $TiCl_4$ adduct of *O*-acryloyl lactate, of which a crystal structure has been determined by Helmchen.[86]

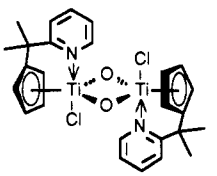
**Chart 13**



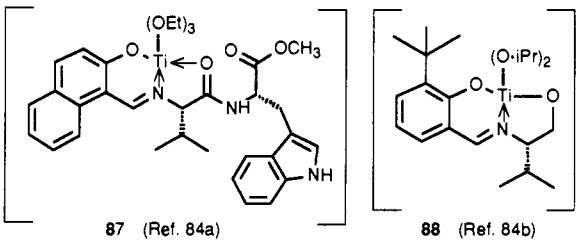

83 (Ref. 80) 84 (Ref. 80)



86 (Ref. 83)



85 (Ref. 82c)



87 (Ref. 84a) 88 (Ref. 84b)

## *III. Addition of d¹-Nucleophiles[5c,d] to Carbonyl Compounds*

### A. Stoichiometric Use of Chiral Alkyl–Titanium Complexes

Chiral methyltitanium reagents can be prepared by two variants as shown in Scheme 11. Displacement of methyl groups by chiral alcohols (R*OH) gives the salt-free reagents **q′** (cf. eq 7 of Scheme 3). Due to the instability of other di-, tri-, and tetraalkyltitanium compounds, this access is limited to methyl reagents. Alternatively, a chiral chlorotitanium complex **q** is transmetalated with MeLi or other alkyllithium, Grignard, or organometallic reagents. Depending on the

Scheme 11

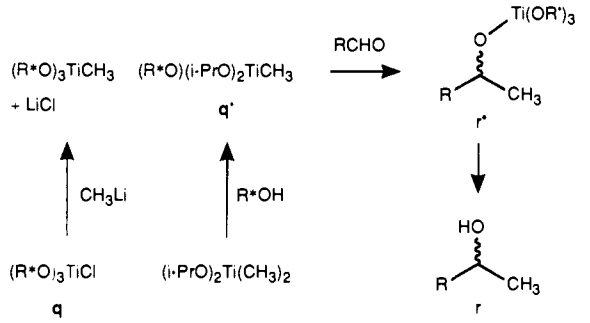



Table 3. Methylation of Aromatic Aldehydes Using Titanium Reagents with Chiral Monodentate Ligands (Cf. Chart 6 and Scheme 11)

| aldehyde | Ti complex no.[a] | Ti complex type[b] | product r: enantiomeric excess,[c] % (config) | ref |
|---|---|---|---|---|
| benzaldehyde | **20** | q | 8 (*S*) | 32a |
| | **21** | q | 12 (*S*) | 32b |
| | **22** | q | 18 (*S*) | 33 |
| | | | 23 (*S*) | 32b |
| | **23** | q | 14 (*S*) | 32b |
| | **24** | q | 10 (*R*) | 32b |
| | **25** | q' | 13 (*S*) | 34 |
| | **26** | q' | 54 (*R*) | 35 |
| 1-naphthaldehyde | **22** | q | 46 (*S*) | 32b |
| | **26** | q' | 30 (*R*) | 35 |
| 2-nitrobenzaldehyde | **22** | q | 76 (*S*) | 32b |

[a] Cf. Chart 6. [b] Cf. Scheme 11. [c] Configuration in parentheses.

conditions, solvent, and precursors, either "ate" complexes, bimetallic aggregates, or if LiCl is precipitated, a pure organotitanium compound is formed. After the reaction with an aldehyde—ketones react at best sluggishly with alkyltitanium compounds[1,2]—the product **r** is obtained by hydrolysis of the titanate **r'**.

The results of methylating benzaldehyde and other simple aromatic aldehydes with **25**, **26**, and the reagents prepared from the chlorotitanates **22–24** (cf. Chart 6) are listed in Table 3. The enantioface discrimination achieved with these reagents is low to mediocre. The best results have been obtained with the tri-*O*-menthyl complex **22** (76% ee)[32b] and with the proline-derived ligand of **26** (54% ee).[35] This rather modest performance might be due to the conformational freedom of complexes with monodentate ligands, or to ligand exchange between the primary products **r'** and the reagents according to equation 6 of Scheme 3.

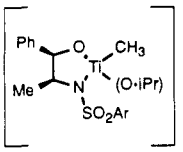
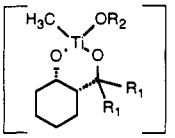
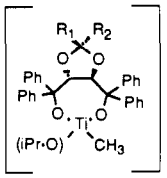
The hope, that the stereoselectivity can be improved with bidentate chiral ligands, was fulfilled largely, as can be seen by inspection of Table 4, listing the results of reagents **57**, **58** (Chart 9), **61a,b** (Chart 10), **67**, **73–75** (Charts 11 and 12). Highlights with an enantiomeric excess exceeding 90% are, however, rare, limited to very specific reagent–substrate combinations. Except for **57** and **58**, which are obtained from $Me_3TiCl$, the exact composition of these reagents is unknown. This is rather unfortunate, since the organometallic precursor of these titanium compounds plays an important role. Furthermore, an undefinable quality of the MeLi solutions causes large variations.[2b,58] Most striking is a reversal from *Si* to *Re* addition reported for the methyl addition to heptanal, if MeLi is exchanged for MeMgBr.[58] This points to a very complicated reaction mechanism, involving solvent-dependent aggregates of organometallic reagents, dependent also on concentration, temperature, salt content, mode of preparation, and substrate structure. Thus, better enantioselectivity is generally obtained for aromatic than for aliphatic or alicyclic aldehydes.[89,90] Replacement of $CH_3$ by other nucleophiles results also in reduced stereoselectivity.

The most reliable process with chiral titanium nucleophiles is the addition of phenyl groups to aromatic aldehydes, using 1,1'-binaphthol as ligand (Scheme 12, Table 5).[32b,66] The resulting diarylmethanols **s** are thereby obtained with optical purities of 90% and better. The induction is lower for aldehydes with ortho substituents and if substituted phenyl nucleophiles are transferred. A most impressive example of practical value is the addition of a highly substituted phenyl group to phytenal, a chiral $\alpha,\beta$-unsaturated aldehyde, affording the vitamin-E precursor **89** with 82% de (Scheme 12).[87] A special case, with the chiral ligand derived from prolinol attached via a sulfonamide linkage to the aryl nucleophile, is the reagent obtained from **90**. Addition to aldehydes gives secondary alcohols, e.g. **91**, with 62–82% de.[88] The diastereoselectivity of the lithiated species is much lower, if the transmetalation to titanium is omitted.

If the tetraalkoxytitanium compounds **76** and **78** are treated with alkyllithium or alkylmagnesium reagents, the formation of "ate" complexes is assumed (see also the results with **66**, Scheme 12, Table 5[66b]). Whatever the nature of the resulting species might be, the methylation of simple aromatic aldehydes is achieved with good enantioselectivity (Scheme 13.[75a,b] In the case of the spirocyclic titanate **78** it could be demonstrated that MeLi gives much better results than Grignard reagents.[75b] Unfortunately no reactions using MeLi have been reported for **76**.[75a] The effect of the second chiral ligand of **78** can therefore not be evaluated (see also below, Scheme 21).

Alkyltitanium complexes with cyclopentadienyl ligands have much higher stability than the analogous complexes with $\eta^1$-bound ligands. Due to reduced Lewis acidity their reactivity is also much lower, and while $Cl_2CpTiCH_3$ still reacts with aldehydes at RT,[91] the dialkoxycyclopentadienylmethyltitanium complexes **92**[78] and **54**,[59a] as well as analogous compounds obtained from **27–29** (Chart 6),[92] are completely unreactive (Scheme 14). This can be overcome by replacing Ti(IV) with Zr(IV) or Hf(IV), as their reactivity is much higher. Alkylzirconium or alkylhafnium compounds, obtained from the chlorides **81** and **82**, are thus reacting with aldehydes even at −78 °C. The enantioselectivity of these reagents is also much higher than of any of the alkyltitanium complexes described above, reaching 97–98% ee for the addition of a methyl group to benzaldehyde. In contrast to the titanium reagents lacking a Cp ligand, Grignard and organolithium compounds give equally good results. However, the enantioselectivity drops to mediocre values, if other alkyl groups than methyl are transferred and nonaromatic aldehydes are methylated less stereoselectively than benzaldehyde.[38b,78]

**Table 4. Methylation of Aldehydes Using Titanium Reagents with Chiral Bidentate Ligands (Cf. Scheme 11)**

| reagent structure | Ti complex no. | Ti complex type[a] | $CH_3M$ | aldehyde | enantiomeric excess,[b] % (config) | ref |
|---|---|---|---|---|---|---|
|  | 58[c] | q′ | | *o*-nitrobenzaldehyde | 90 (*R*) | 59b |
| | 58[c] | q′ | | benzaldehyde | 88 (*R*) | 59b |
| | 57[c] | q′ | | benzaldehyde | 85 (*R*) | 59b |
| | 57[c] | q′ | | octanal | 60 (*R*) | 59b |
| | 57[c] | q′ | | 2-ethylbutanal | 73 (*R*) | 59b |
|  | 61b[d] | q | $CH_3MgCl$ | 1-naphthaldehyde | 96 (*S*) | 58 |
| | 61a[d] | q | $CH_3MgCl$ | 1-naphthaldehyde | 94 (*S*) | 58 |
| | 61a[d] | q | $CH_3MgCl$ | benzaldehyde | 58 (*S*) | 58 |
| | 61a[d] | q | $CH_3MgCl$ | nonanal | 58 (*S*) | 58 |
| *cf.* Chart 11 | 67[e] | q | $CH_3Li$ | benzaldehyde | 59 (*S*) | 32b |
|  | 73[f] | q | $CH_3MgCl$ | benzaldehyde | 42 (*S*) | 58 |
| | 74[f] | q | $CH_3MgCl$ | benzaldehyde | 75 (*S*) | 58 |
| | 75[f] | q | $CH_3MgCl$ | benzaldehyde | 65 (*S*) | 58 |
| | | | $CH_3Li$ | benzaldehyde | 49[g] (*S*) | 58 |
| | | | $[Me_4B]Li$ | benzaldehyde | 76 (*S*) | 58 |
| | 73[f] | q | $CH_3Li$ | heptanal | 83 (*S*) | 58 |
| | | | $CH_3MgBr$ | heptanal | 38 (*R*) | 58 |
| | 75[f] | q | $CH_3Li$ | heptanal | 42 (*S*) | 58 |

[a] Cf. Scheme 11. [b] Configuration in parentheses. [c] Cf. Chart 9. [d] Cf. Chart 10. [e] Cf. Chart 11. [f] Cf. Chart 12. [g] 91% ee were obtained in an irreproducible experiment with $CH_3Li$ of unknown quality.

**Scheme 12**

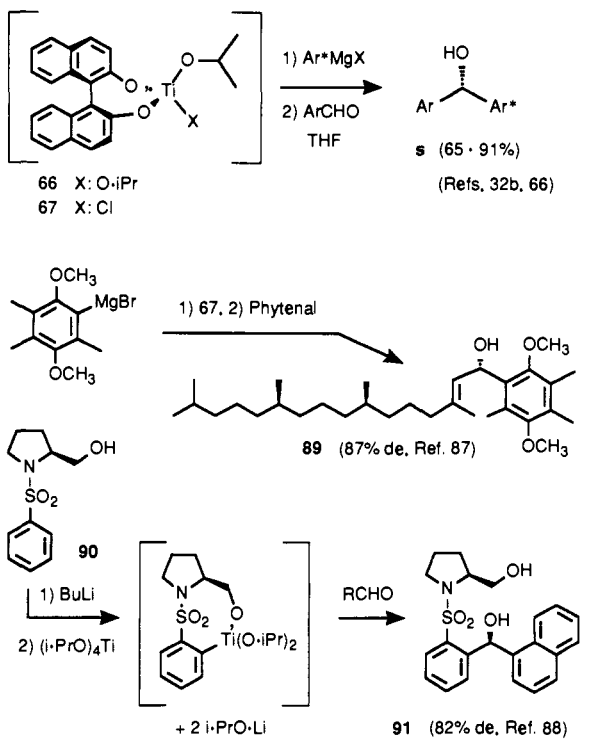


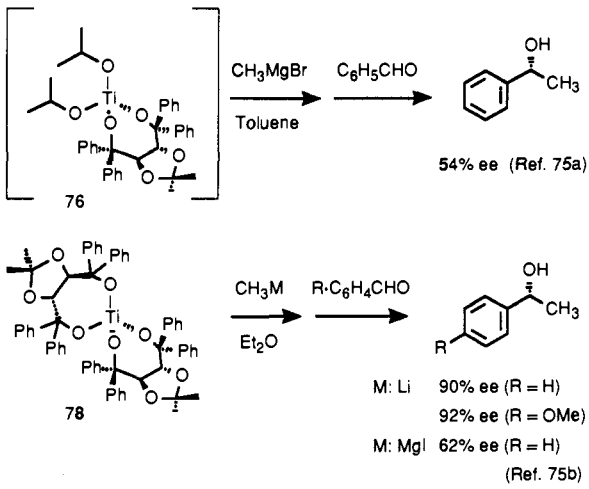

**Table 5. Enantioselective Synthesis of Unsymmetrical Diarylmethanols s, Using 1,1′-Binaphthyl Titanates 66 and 67 (Cf. Scheme 12)**

| complex | Grignard reagent: Ar* | aldehyde: Ar | enantiomeric excess, % | ref |
|---|---|---|---|---|
| 67 | phenyl | 4-$MeOC_6H_4$ | 82 | 66a |
| 67 | phenyl | 4-$MeC_6H_4$ | 88 | 32b |
| 67 | phenyl | 4-$ClC_6H_4$ | ≥95 | 66b |
| 67 | phenyl | 4-$NO_2C_6H_4$ | 76 | 66a |
| 67 | phenyl | 4-$NO_2C_6H_4$ | 88 | 66b |
| 66 | phenyl | 4-$NO_2C_6H_4$ | 90 | 66b |
| 67 | phenyl | 2-$MeOC_6H_4$ | 95 | 66b |
| 67 | phenyl | 2-$PrOC_6H_4$ | 7 | 66b |
| 66 | phenyl | 2,6-$(MeO)_2C_6H_3$ | 25 | 66b |
| 67 | phenyl | 2-$NO_2C_6H_4$ | 39 | 66a |
| 67 | phenyl | 1-naphthyl | 98 | 66a |
| 67 | phenyl | 2-naphthyl | 98 | 66a |
| 67 | phenyl | 9-anthracenyl | 69 | 66a |
| 67 | 2-fluorophenyl | 1-naphthyl | 89 | 66a |
| 67 | 2-naphthyl | phenyl | 46 | 66a |

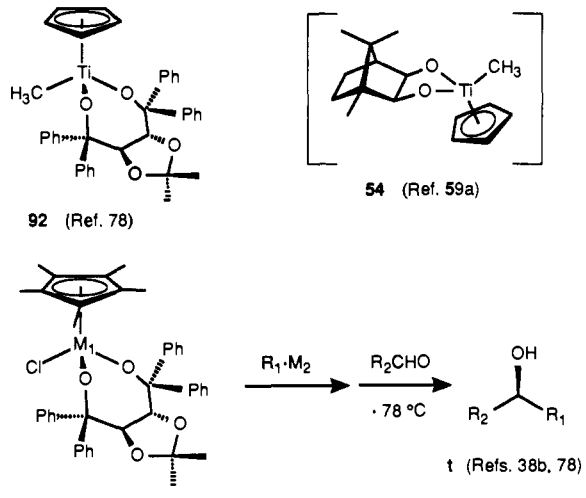
## B. Chiral Titanium Complexes as Catalysts for Enantioselective Additions Using Dialkylzinc Compounds

The enantioselective addition of dialkylzinc compounds to aldehydes, mediated by a catalytic amount of a chiral amino alcohol is considered a breakthrough in asymmetric synthesis.[6c,d,93] It was soon found that the actual catalyst of this process is not the amino alcohol itself, but a zinc chelate formed in situ from the zinc reagent and amino alcohol. As a consequence the variety of new catalyst systems increased, and Li salts[94] or boron compounds[95] derived from such amino alcohols were introduced as mild Lewis acids, replacing the original zinc complexes. Still farther away from the original amino alcohols is the combination of 0.3–1.2 equiv of $(i\text{-PrO})_4Ti$ with 0.5–4 mol % of a chiral bis-sulfonamide ligand, introduced by Yoshioka and coworkers as a very efficient catalyst for $Et_2Zn$ alkylations (Scheme 15).[60] Even if $(i\text{-PrO})_4Ti$ can activate $Et_2Zn$ to some extent, the essential rate acceleration is due to the chiral bis-sulfonamide. As this ligand alone cannot act as a catalyst, the formation of a titanium complex (**59**, Chart 9) has to be assumed.[60a] NMR analysis of such mixtures revealed that strong aggregates are formed between $Et_2Zn$ and titanium complexes. The original $Et_2Zn$ signals disappear, and it is reasonable to assume that at least part of the alkylzinc substituents are transferred to titanium, since the titanium–carbon bonds are much stronger than zinc–carbon bonds.[96] The aggregate **93** (Scheme 15) was postulated as a hypo-

**Scheme 13**

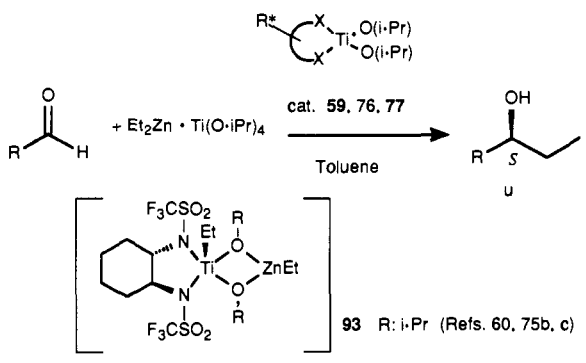



**Scheme 14**




| | | | |
|---|---|---|---|
| 81 $M_1$: Zr | $CH_3MgBr$ | $R_2$: $C_6H_5$ | **98% ee** |
| | $CH_3Li$ | $R_2$: $C_6H_5$ | **97% ee** |
| | EtMgBr | $R_2$: $C_6H_5$ | 52% ee |
| | n-BuLi | $R_2$: $C_6H_5$ | 68% ee |
| | $CH_3Li$ | $R_2$: $C_9H_{19}$ | **80% ee** |
| 82 $M_1$: Hf | $CH_3MgBr$ | $R_2$: $C_6H_5$ | **97% ee** |
| | EtMgBr | $R_2$: $C_6H_5$ | 47% ee |
| | n-BuLi | $R_2$: $C_6H_5$ | 65% ee |

**Scheme 15**




thetical reactive species of this catalytic cycle.[60] At the present stage of investigation it is, however, still not clear whether a titanium- or zinc-bound alkyl substituent is transferred to the aldehyde carbonyl. While it is evident, that complex **59** with an electron-deficient nitrogen ligand is a stronger Lewis acid for the activation of $Et_2Zn$ than $(i\text{-PrO})_4Ti$, it was amazing to learn from recent reports of Seebach and co-workers, that tetraalkoxytitanium complexes **76** and **77** with bulky tartrate-derived ligands (Chart 12) can activate $Et_2Zn$ better than $(i\text{-PrO})_4Ti$ and are therefore excellent chiral catalysts for aldehyde ethylations.[75b,c] It could be that the bulky ligands of **76** and **77** impede self-aggregation, as opposed to $(i\text{-PrO})_4Ti$, and that complexation of smaller molecules like $Et_2Zn$ is therefore facilitated. Narasaka and co-workers have already observed in a different context, that the closely related titanate **72** (Scheme 9) appears to be "a stronger Lewis acid than $(i\text{-PrO})_4Ti$".[10b]

The results of the $Et_2Zn$ additions catalyzed by titanium complexes are compiled in Table 6. As far as comparisons are possible, complexes **59**[60] and **77**[75c] appear to be somewhat superior to **76**.[75b] Excellent inductions (91–99% ee) are thus obtained even in reactions with nonaromatic substrates. Good results with aliphatic aldehydes have, however, been reported recently for amino alcohol catalysis as well.[93h,n-p,94a]

With rare exceptions[87] this promising method has so far been restricted to transformations of purely academic interest. One reason is the lack of a general and easy access to dialkylzinc compounds. In addition to the ubiquitous $Me_2Zn$ and $Et_2Zn$ only butyl,[94c] pentyl,[97a] vinyl,[93h,r] and (2-furyl) groups[97b] could be transferred until recently. However, Knochel reported recently that even functionalized diorganozinc compounds can be prepared by reaction of primary iodides and diethylzinc.[98] Another breakthrough was reported by Seebach and co-workers.[99] On the basis of the observation that ether can be used as solvent in case of the titanium catalyst **76** (cf. Table 6, entry 2), various dialkylzinc reagents have been prepared from Grignard solutions and $ZnCl_2$ in $Et_2O$, upon precipitation of $MgCl_2$ as its dioxane complex and filtration (Scheme 16). These solutions can then be used directly for reactions with aldehydes, catalyzed by the chiral titanate **76** and $(i\text{-PrO})_4Ti$.[99] With this modification the scope of this method has been considerably extended. Limitations are mainly due to steric influences, as slow reactions and low yields are observed for alkyl nucleophiles with branched β-carbons. In the case of hindered substrates like pivalaldehyde and α-branched dialkylzinc compounds the stereoselectivity is low as well (Scheme 16). At the moment it is not clear, whether this Grignard variant is restricted to titanium catalysis. Hydrocarbons are used in most cases of catalysis by amino alcohols. However, successful reactions in hexane/$Et_2O$,[93e] toluene/$Et_2O$,[93q,94c] $Et_2O$,[93f] and even THF[87] have been reported as well.

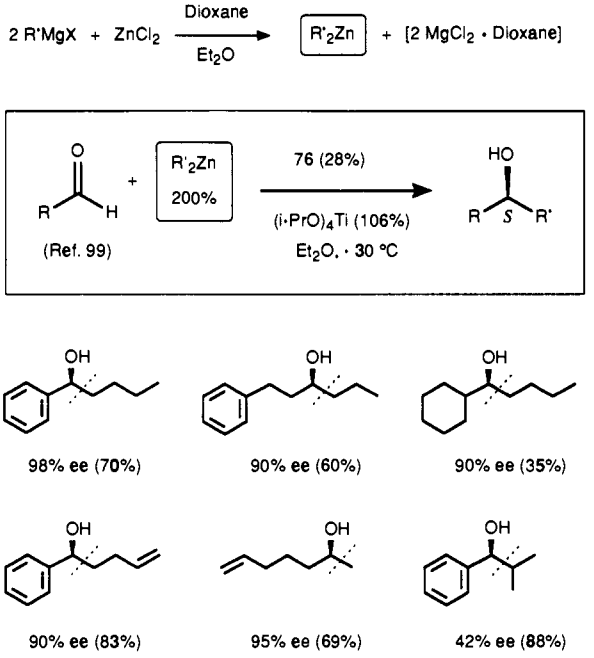
Without $(i\text{-PrO})_4Ti$ chiral titanium complexes can mediate the enantioselective alkylation of aldehydes with dialkylzinc compounds as well. As shown in Scheme 17 for the spirocyclic titanate **78**, these reactions are usually sluggish and an excess of **78** (200%) has to be used for complete conversion and high enantioselectivity.[75b] While *Si* addition is induced by the monocyclic complex **76** with $(i\text{-PrO})_4Ti$, the spirocyclic **78** alone is favoring the *Re* attack. It is clear that the mechanism of these titanium-mediated dialkylzinc additions still needs to be clarified if the enantioface

**Table 6. Ethylation of Aldehydes with $Et_2Zn/(i\text{-}PrO)_4Ti$, Catalyzed by the Titanates 59, 76, and 77 (Scheme 15, refs 60 and 75b,c)**

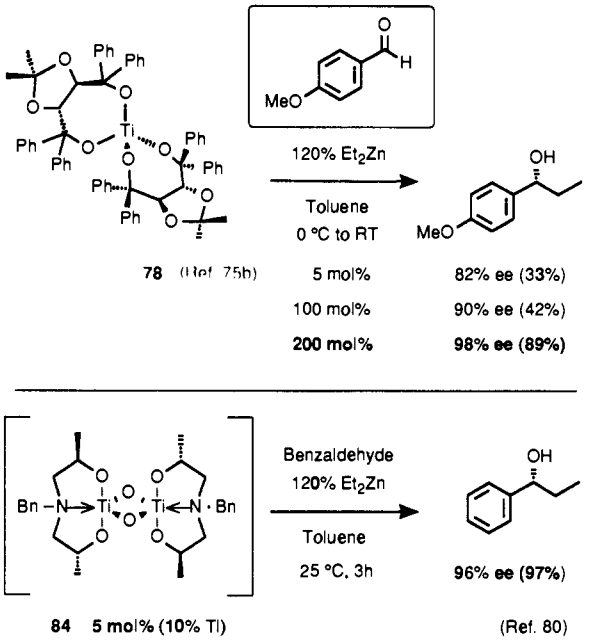
| aldehyde: R | [L*]Ti(OR)$_2$: no. (mol %) | $Et_2Zn$, mol % | $Ti(OR)_4$, mol % | T, °C | product u: yield, % | product u: enantiomeric excess, % (config) | ref |
|---|---|---|---|---|---|---|---|
| $C_6H_5$ | **59** (0.5) | 120 | 120 | 0 | 96 | 99 (*S*) | 60a |
| $C_6H_5$ | **76** (20) | 120 | 120 | -75 to 0 | 75[a] | 99[a] (*S*) | 75b |
| $C_6H_5$ | **77** (5) | 180 | 120 | -25 | 95 | 92 (*S*) | 75c |
| $C_6H_5CH{=}CH$ | **59** (2) | 220 | 30 | -50 | 85 | 99 (*S*) | 60b |
| $C_6H_5CH{=}CH$ | **77** (5) | 180 | 120 | -25 | 87 | 91 (*S*) | 75c |
| $C_6H_5C{\equiv}C$ | **77** (5) | 180 | 120 | -25 | 83 | 99 (*S*) | 75c |
| $C_6H_5CH_2CH_2$ | **59** (1) | 220 | 60 | 0 | 95 | 92 (*S*) | 60b |
| $C_6H_5CH_2CH_2$ | **76** (20) | 120 | 120 | -75 to 0 | 82 | 85 (*S*) | 75b |
| $C_6H_5CH_2CH_2$ | **77** (5) | 180 | 120 | -25 | 87 | 98 (*S*) | 75c |
| $CH_3(CH_2)_4$ | **59** (4) | 220 | 60 | -20 | 78 | 99 (*S*) | 60b |
| $CH_3(CH_2)_5$ | **76** (20) | 120 | 120 | -75 to 0 | 75 | 92 (*S*) | 75b |
| $CH_3(CH_2)_5$ | **77** (5) | 180 | 120 | -25 | 70 | 97 (*S*) | 75c |
| cyclohexyl | **76** (20) | 120 | 120 | -75 to 0 | 67 | 82 (*S*) | 75b |
| cyclohexyl | **77** (5) | 180 | 120 | -25 | 77 | 99 (*S*) | 75c |

[a] In $Et_2O$ the yield is 62% and the enantiomeric excess is 98% (ref 75b).

**Scheme 16**




**Scheme 17**




discrimination should be understood. At least one function of the $(i\text{-}PrO)_4Ti$ is, however, clear: reactivation of the chiral catalyst by replacing the product alkoxide with isopropoxide. This is, however, not mandatory for such catalysts. The chiral titanium oxide **84**, recently prepared by Nugent, is a very efficient catalyst for the ethylation of benzaldehyde *without* $(i\text{-}PrO)_4Ti$ (Scheme 17).[80] This is a preliminary result, and it is not clear yet whether the replacement of two alkoxide ligands by a polynuclear oxide structure or the additional amine coordination is responsible for this very promising property of **84**. The rather slim shape of this novel titanium ligand also demonstrates that bulky groups are not a necessity for good asymmetric induction.

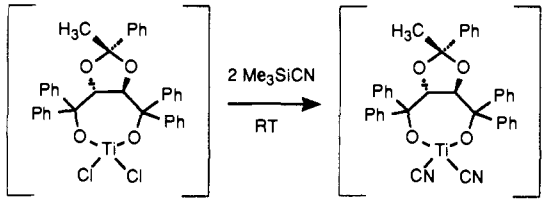
These exciting new developments show, that the catalytic asymmetric carbonyl alkylation with dialkylzinc compounds has already reached an impressive synthetic potential. The next step will be to test the compatibility with more complex and especially with functionalized substrates.

## C. Titanium-Mediated Addition of Other Nucleophiles than Alkyl or Aryl Groups

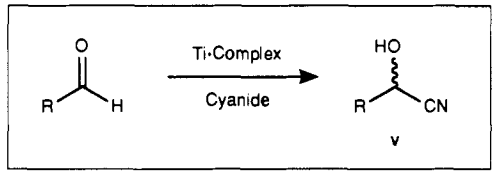
Titanium complexes can effect the addition of $Me_3SiCN$ or HCN to aldehydes. As shown in Scheme 18 and Table 7, optically active cyanohydrins **v** are obtained, if chiral titanium complexes are used. In case of the complexes **65**[65a] and **71**[10a] chloride substitution could afford cyanotitanium reagents. Narasaka and co-workers could demonstrate with the aid of NMR, that such a cyanide exchange occurs only, if **71** and $Me_3SiCN$ are warmed to RT (**94**, Scheme 18).[100] While stoichiometric quantities of the reagent **65**, **71**, and **94** are needed, the modified Sharpless catalyst **50**,[101] the dipeptide–$Ti(OEt)_4$ complex **87**,[84a] and **88**[84b] can be used catalytically. The asymmetric induction of these reactions is quite appealing (57–97% ee), and if catalysis is not the main objective, the tartrate-derived complexes **71** and **94**[100] appear to give the best results.

The complex **72** (Scheme 9) has been used as an enantiomer selective catalyst for the transesterification of racemic (2-pyridyl) thiol esters **w** (Scheme 19).[10b] In

Scheme 18

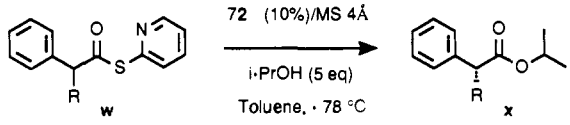



71 94 (Ref. 100b)




v

Scheme 19




w x

(Ref. 10b) R: Et 92% ee (69%)
R: i-Pr 94% ee (44%)

the case of 2-arylalkanoates the optical purity of the (*R*)-configurated isopropyl esters x, obtained in 37–78% yield, is excellent (88–94% ee).

## *IV. Addition of d³-Nucleophiles[5c,d] to Carbonyl Compounds*

### A. Enantioselective Allyltitanation of Aldehydes

The regio- and stereoselective allylmetalation of aldehydes is synthetically very useful, as acyclic structures with one or two new stereogenic centers can be obtained.[102] Many possibilities for further transformations are provided by the double bond, and depending on the substitution, these reagents can be considered as aldol[102a,c,d] or homoaldol synthons.[102e] With achiral allyltitanium reagents impressive regio- and diastereocontrol could be achieved.[1,2,103] A six-center cyclic transition state **c** (Scheme 2) with chair conformation[8] explains the diastereoselectivity and also accounts for the higher reactivity of allyltitanium compounds, when compared to the alkyl counterparts. Therefore Cp- and even $Cp_2$-substituted complexes can be used (see below), and ketones can be allylated with high diastereocontrol as well.[104]

Excellent enantioface control of nucleophilic additions to carbonyl groups is possible, if the chirality is incorporated in the nucleophilic ligand. In the case of *O*-enolates of carboxylic acid derivatives, chiral auxiliaries can be attached via ester or amide linkages. This approach is generally not possible for allylic nucleophiles. However, the $\alpha$-carbon of substituted allyl ligands is a stereogenic center, and if its configuration can be controlled, highly stereoselective reagents result. The metalation of an allyl urea affording **39** is controlled by a covalently bound auxiliary (cf. Scheme 6).[42] Due to a transition state of defined geometry, the chirality of **39** is transferred efficiently to the carbonyl substrates. An especially impressive example is the addition of isopropyl methyl ketone, giving **95** with 96% de (Scheme 20). Hoppe and co-workers have prepared similar reagents without covalently bound auxiliaries.[40] The enantiomeric reagents **32** and **33** are derived from the same optically active allyl carbamate (cf. Scheme 5).[40a] Addition to isobutyraldehyde gives **96** and its enantiomer *ent*-**96** with excellent diastereoselectivity and moderate to good enantioselectivity (Scheme 20). The chiral titanium complex **37** is derived from a prochiral allyl carbamate. A chiral ligand (sparteine) was therefore used for the enantiotopic metalation (cf. Scheme 5).[40b] The stereoselectivity of **37** lacking the methyl substituent at C(1) is much better, and the lactaldehyde adduct **97** is obtained with high enantiomeric purity (>95% ee, Scheme 20).

Allyltitanium complexes lacking cyclopentadienyl ligands are very reactive. This does not affect the diastereoselectivity of crotyl reagents,[103,104] but the enantioface selectivity is difficult to control with chiral titanium ligands. So far the best results have been reported for the complexes **75**, **76**, and **78**, all with similar, tartrate-derived ligands (cf. Chart 12). As shown in Scheme 21 for the allylation of benzaldehyde, the induction is low (34% ee), if an allyltitanium reagent is prepared from the chloride **75**.[58] Better selectivity (54 and 60% ee) is obtained with "ate" complexes derived from the tetraalkoxides **76**[75a] and **78**.[75b] It is interesting to note, that the replacement of the (*i*-PrO) ligands by another chiral chelate ring reverses the induction from *Si* face addition (**76**) to *Re* face preference (**78**). Strangely enough, this is not the case for methyl-group transfer and *Re* addition is observed for **76** and **78** (cf. Scheme 13).

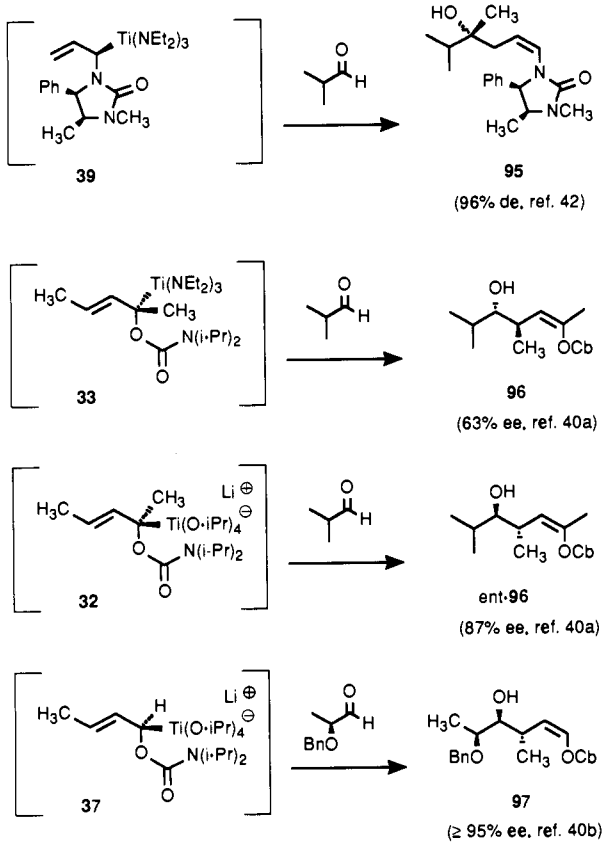
Monocyclopentadienyltitanium complexes with chiral ligands emerged as much better templates for the enantioselective allyltitanation of aldehydes. The Lewis acidity and therefore also the reactivity and tendency to aggregation is considerably reduced for cyclopentadienyl-substituted compounds. This appears to be an important prerequisite for a clean bimolecular reaction path. Interestingly no defined allyl reagent could be obtained from the camphanediol complex **53**.[59a] Readily prepared by transmetalation of the chlorides **27** (Chart 6),[36a] **48**, **49**, and **80** (Scheme 10)[38,39a] with allylmagnesium chloride are, however, the allyltitanium compounds **98–101** (Scheme 22). The enantioface differentiation of allyltitanations with these reagents is generally better than 95:5 (90% ee). While *Re* addition is obtained with D-glucose as chiral auxiliary, *Si* attack is favored with 1,4-dihydroxy ligands derived from (*R,R*)-tartrate. Allyl reagents prepared from the chlorides **28** or **29** (Chart 6) with different acetal protection of their glucose ligands show similar stereoselectivity as **98**, but compounds with undefined structure, like the L-idose complex **30**, afford, according to a quite general rule, also unselective reagents.[37,38] In the case of the tartrate-derived ligands the influence of the acetal groups on the stereoselectivity is low, and replacement of the acetonide of reagent **99** by other substituents gave inductions ranging from 80% ee for the 2,2-unsubstituted dioxolane to 91% ee with the bulky fluorenone acetal.[39a] In contrast to other applications of such ligands,[58,105] unsymmetrically substituted dioxolanes, like the pivalaldehyde acetal, have

**Table 7. Enantioselective Cyanohydrine Formation with Chiral Titanium Complexes (Scheme 18)**

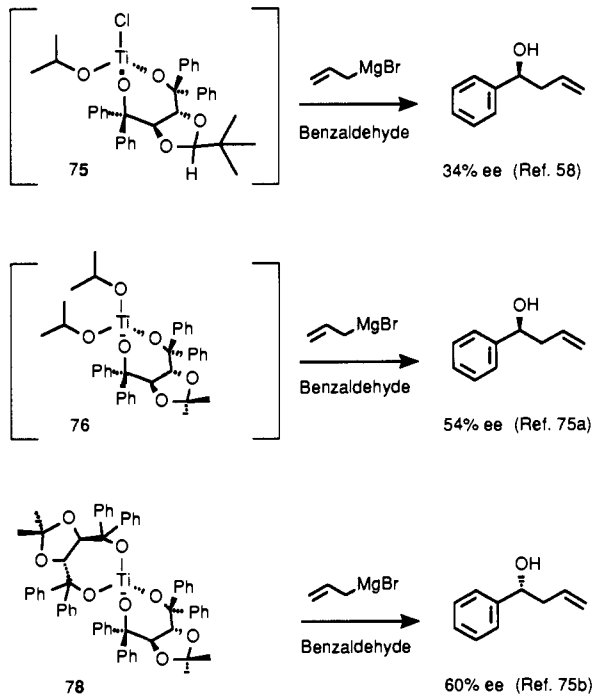
| aldehyde | Ti complex | cyanide source | product v: enantiomic excess, % (config) | ref |
|---|---|---|---|---|
| isovaleraldehyde | **65**[a] | $Me_3SiCN$ | 88 | 65a |
| benzaldehyde | **71**[b]/MS 4 Å | $Me_3SiCN$[c] | 96 (*R*) | 100 |
| benzaldehyde | **94**[d] | $Me_3SiCN$[e] | 73 (*R*) | 100b |
| 3-phenylpropionaldehyde | **71**[b]/MS 4 Å | $Me_3SiCN$[c] | 74 (*R*) | 100b |
| 3-phenylpropionaldehyde | **94**[d] | $Me_3SiCN$[e] | 97 (*R*) | 100b |
| benzaldehyde | **50**[f] (20%) | $Me_3SiCN$ | 91[g] (*R*) | 101 |
| benzaldehyde | **87**[h] (10%) | HCN | 88 (*R*) | 84a |
| cyclohexanecarbaldehyde | **87**[h] (10%) | HCN | 54 (*R*) | 84a |
| heptanal | **87**[h] (10%) | HCN | 74 (*R*) | 84a |
| *p*-methoxybenzaldehyde | **88**[h] (20%) | $Me_3SiCN$[i] | 91 (*R*) | 84b |
| cyclohexanecarbaldehyde | **88**[h] (20%) | $Me_3SiCN$[i] | 65 (*R*) | 84b |
| dodecanal | **88**[h] (20%) | $Me_3SiCN$[i] | 66 (*R*) | 84b |

[a] Chart 11. [b] Scheme 9. [c] Reaction in toluene at −65 °C. [d] Scheme 18. [e] Reaction in toluene at −78 °C. [f] Modified Sharpless catalyst (Chart 9). [g] Isolated as silyl ether. [h] Chart 13. [i] Reaction in $CH_2Cl_2$ at −78 °C.

**Scheme 20**




**Scheme 21**

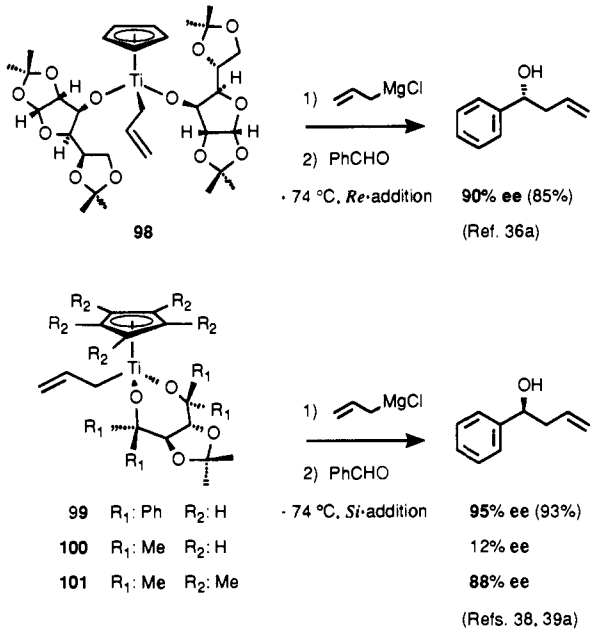



no beneficial effect on the stereoselectivity. On the contrary, mixtures of diastereomeric complexes are obtained as a result of the prochiral substitution of titanium.

A decisive influence is, on the other hand, exerted by the substituents of the carbinol groups. The enantioselectivity of **99** (95% ee) is almost completely lost, if the four phenyl groups of the ligand are replaced by methyls (reagent **100**, 12% ee). A very interesting synergism between the chiral chelating ligand and the cyclopentadienyl substituent is responsible for the fact that very good enantioselectivity can also be obtained, if the small tetramethylthreitol ligand is combined with the bulky pentamethylcyclopentadienyl group (reagent **101**, 88% ee).

Some insight into possible mechanisms of asymmetric induction can sometimes be gained from crystal structure analyses. ORTEP plots ("side views") of the structures **27** (*Re* preference, Chart 6),[36b] **48** (unselective, Scheme 10), and **49** (*Si* preference, Scheme 10)[38,39a] are therefore shown in Figure 1 (the corresponding "front views" can be found in refs 36b, 38, and 39a). The two diacetone glucose ligands form indeed a highly asymmetric environment ("chiral pocket") around the titanium–chloride bond of **27**. NMR measurements support a rather rigid structure (low-energy conformer) in solution. A NOE of one of the eight acetonide methyl groups with the Cp ligand could correspond to the 5,6-dioxolane ring of one sugar ligand shielding the *Re* side of the Cl–Ti–$Cp_{centroid}$ plane, as seen in the X-ray structure of **27**. The energetic preference of this conformer could, however, not be corroborated by force field calculations, as the conformation with the 5,6-dioxolane of the other glucose ligand shielding the *Si* side of the Cl–Ti–$Cp_{centroid}$ plane converged at a similar energy.[38,51] It is therefore an open question, whether the preference of such a conformer is responsible for the high stereoselectivity achieved with reagents derived from **27**. Such steric arguments appear even more doubtful, if the structure of **49** is considered. Not only is the Ti–Cl bond sterically uncongested, but the four

**Scheme 22**




phenyl substituents are arranged symmetrically to the Cl–Ti–$Cp_{centroid}$ plane. A $C_2$ symmetrical or skew conformation, which is often considered essential for the transmission of chirality,[72d,105,106] is clearly not exhibited by chloride **49**, the precursor of highly stereoselective reagents (cf. Schemes 22 and 23 and Table 8). When compared with the unselective complex **48**, the most pronounced difference is the steric interaction between the Cp ring and the *syn*-phenyl substituents, by which the chelate ring of **49** is forced away from the Cp ligand. The Cl–Ti→C(2) angle of 123° (**48**) is thereby reduced to 103° (**49**).[39a] A similar distortion can be expected for complex **80** (*Si* preference, Scheme 10), the pentamethylcyclopentadienyl analog of **48**. An X-ray structure determination is, however, not yet available.

These ligand–ligand interactions could in principle also induce chiral distortions of the coordination geometry. Such an effect is clearly exhibited by the two Ti–O–C($\alpha$) bond angles of **27** and **49** but not of the unselective reagent precursor **48** (cf. Table 1 and discussions in refs 38 and 39a). This oxygen distortion could also affect the titanium, as a more obtuse bond angle at oxygen allows for an enhanced back-bonding of the oxygen lone pairs. This is not reflected by different Ti–O bond lengths (cf. Table 1), but by titanium NMR. The symmetry of the electron distribution at Ti can be assessed qualitatively, but with high sensitivity, by the $^{49}$Ti line width, which is broadened considerably by electronic dissymmetry.[38b,39a,107] Much broader lines were indeed observed for the distorted structures **27** ($\nu^{1/2} \geq 4500$ Hz) and **49** ($\nu^{1/2} = 3460$ Hz) than for **48** ($\nu^{1/2} = 1080$ Hz).[39a] The qualitative correlation of enantioselectivity with the electronic distortion of **27**, **48**, and **49** as measured by X-ray and $^{49}$Ti NMR may reflect a causal relation as well, especially if direct steric interactions of the chiral ligand with the reaction centers are difficult to detect, as in the case of **49**. Similar arguments have been used recently by Faller and co-workers for explaining the stereoselectivity of a chiral crotylmolybdenum reagent.[108]

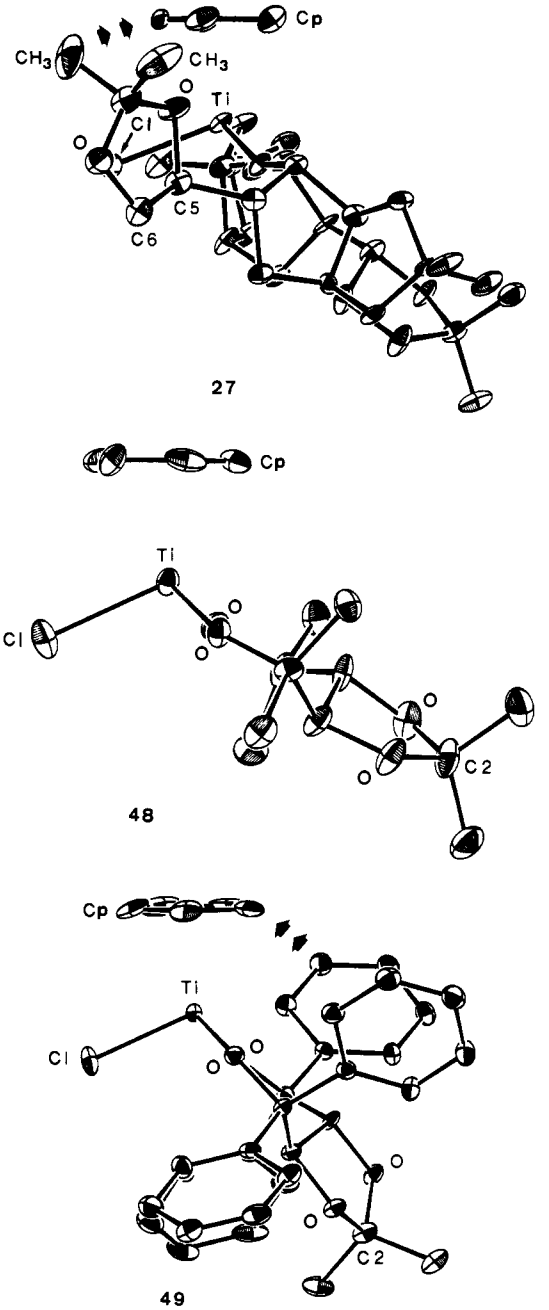



**Figure 1.** ORTEP plots, vibrational ellipsoids at the 20% probability level, of **27**, **48**, and **49** (cf. Chart 6 and Scheme 10 and refs 36b and 39a).

The chlorides **27** and **49** can also be used for the transmetalation of substituted anionic allyl reagents. Reaction with aldehydes **y** gives exclusively the branched regioisomers **z** with anti configuration and high optical purity (*Si* addition, if **49** is used, Scheme 23).[36a,38,39a] Most interestingly, this result is not dependent on the regioisomeric purity or cis/trans isomerism of the allyl precursor used, i.e. typical Grignard mixtures[109] can be used, as well as defined species obtained by allylic metalation.[110] The $^1$H and $^{13}$C NMR spectra of the crotyl reagent **102** showed that the trans isomer with titanium bound to the unsubstituted allyl terminus is always formed. This is due to a fast 1,3-isomerization of these $\eta^1$-bound allytitanium complexes. In the $^1$H NMR spectrum of the allyl complex **99** (Scheme 22) only one signal is observed for all four terminal allyl protons. This degeneracy of the NMR persists down to −100 °C, even for the $^{13}$C NMR spectrum of **99**.[39a] Other isomers,

**Scheme 23**

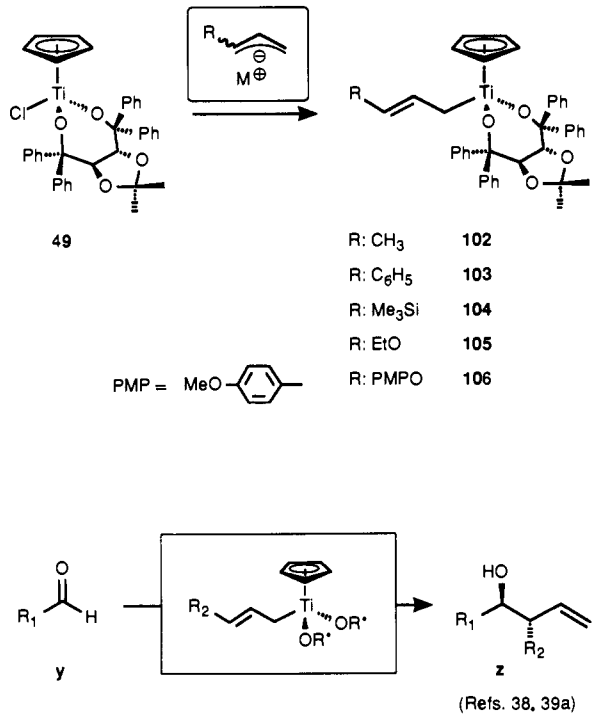



**Table 8. Dia- and Enantioselective Allyltitanation of Aldehydes y with the Reagents 99 and 102–106 (Scheme 23, refs 38 and 39a)**

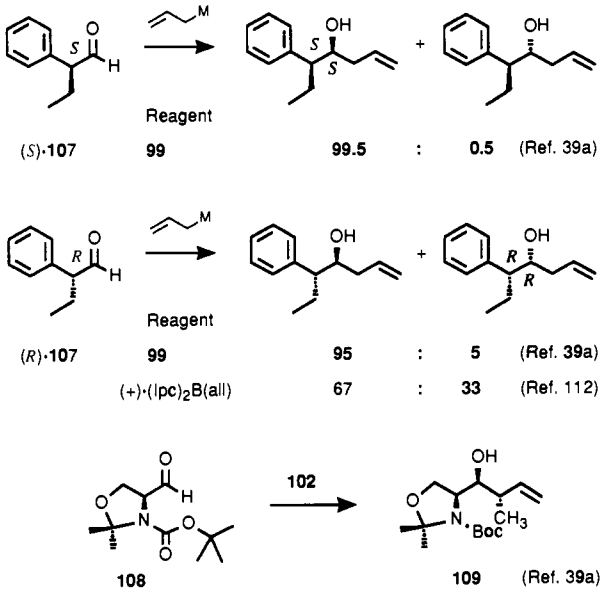
| aldehyde y: $R_1$ | reagent no. | reagent $R_2$ | enantiomeric excess, % | diastereomeric excess, % | yield of z, % |
|---|---|---|---|---|---|
| $C_6H_5$ | **99** | H | 95 | | 93 |
| $CH_3(CH_2)_8$ | **99** | H | 94 | | 92 |
| $(CH_3)_2CH$ | **99** | H | 97 | | 90 |
| $(CH_3)_3C$ | **99** | H | 97 | | 86 |
| $CH_2{=}CH$ | **99** | H | 95 | | 86 |
| $C_6H_5$ | **102** | $CH_3$ | 98 | 97 | 89 |
| $C_6H_5$ | **103** | $C_6H_5$ | 97 | ≥98 | 54 |
| $C_6H_5$ | **104** | $Me_3Si$ | ≥98[a] | ≥98[a] | 68 |
| $C_6H_5$ | **105** | EtO | 95 | 75 | 77 |
| $C_6H_5$ | **106** | PMPO[b] | ≥98[a] | ≥98[a] | 93 |
| $CH_3(CH_2)_8$ | **102** | $CH_3$ | ≥98[a] | ≥98[a] | 86 |
| $CH_3(CH_2)_8$ | **104** | $Me_3Si$ | ≥98[a] | ≥98[a] | 68 |
| $CH_3(CH_2)_8$ | **105** | EtO | 92 | 94 | 73 |
| $CH_3(CH_2)_8$ | **106** | PMPO[b] | ≥95[c] | ≥95[c] | 69 |

[a] Only one isomer was detected by capillary GLC (Chirasil-Val). [b] PMP: *p*-methoxyphenyl. [c] Determined by $^1H$ NMR with 2,2,2-Trifluoro-1-(9′-anthracenyl)ethanol (TFAE).

and therefore also the products with syn configuration, are therefore not accessible with this method.

The results of the allytitanation of aldehydes **y** with the reagents **99** and **102–106** are listed in Table 8. Experiments with the diacetone glucose reagent **98** (Scheme 22) and other allyl-compounds prepared from chloride **27** (Chart 6) are omitted. The selectivities are very good as well, but still somewhat lower, when compared with reagents derived from **49**. If price does not play a major role, *Re* addition can be induced with the enantiomeric reagents derived from (*S*,*S*)-tartrate. These reactions generally proceed with acceptable to very good yields, and the products are formed with exceptionally high stereoselectivities (enantiomeric and diastereomeric excess of 95–98%).[39a] The conversion of benzaldehyde with the ethoxy-substituted allyl reagent **105** is an exception, as ca. 12% of syn epimer is obtained. This problem is avoided by the use of reagent **106** with a bulky *p*-methoxyphenyl substituent. This alcohol protecting group can furthermore be removed readily by oxidation with cerium(IV) ammonium nitrate (CAN).[39a]

**Scheme 24**

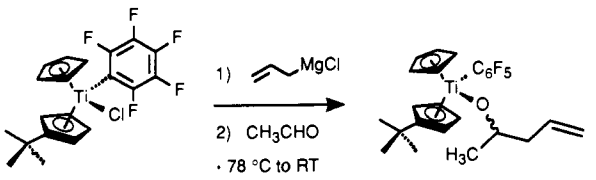



Allyltitanium reagents derived from chiral dialkyl cyclopentadienylchlorotitanates give excellent results with more complex substrates as well, as exemplified by conversions of chiral aldehydes with **99** and **102** (Scheme 24). Nucleophilic additions to α-phenylbutyraldehyde **107** follow with high preference the Cram's rule,[111] affording the (*S*,*S*) or (*R*,*R*) diastereomers. It is therefore difficult to obtain the epimers by reagent control. As expected, the stereoselectivity is excellent for matched combinations, and the diastereomeric excess obtained from the transformation of (*S*)-**107** with the chiral allyltitanium reagent **99** is 99%. Astonishing is, however, the 95:5 ratio (90% de) of the mismatched reaction with (*R*)-**107**, especially if compared with the 34% de obtained with diisopinocampheylborane,[112] one of the best allylboron reagents. Reaction of the protected serine aldehyde **108**[113] with the crotyltitanium complex **102** affords the anti diastereomer **109** in isomerically pure form, according to NMR and capillary GLC (Scheme 24).[39a]

From these results it is clear, that chirally modified cyclopentadienyltitanium complexes afford excellent allyl transfer reagents, which are among the most efficient known. They compete favorably with allylboron reagents,[114] with respect to stereoselectivity and ease of preparation. Substituted allyl nucleophiles always give exclusively the anti diastereomers. For the preparation of syn isomers the allylboron reagents are the best choice. All these reactions use stoichiometric amounts of chiral auxiliaries. A very promising development is therefore the addition of allylsilanes catalyzed by a chiral (acyloxy)borane, reported recently by Yamamoto and co-workers.[115]

The allyltitanations with chiral titanocene derivatives studied so far are again less successful than the monocyclopentadienyl reagents described above. One reason might be that the reactivity of this class of compounds is very much reduced by the influence of two $\eta^5$-bound ligands. An interesting reagent is derived from chloride **4** (Scheme 4) with an asymmetric titanium center. A

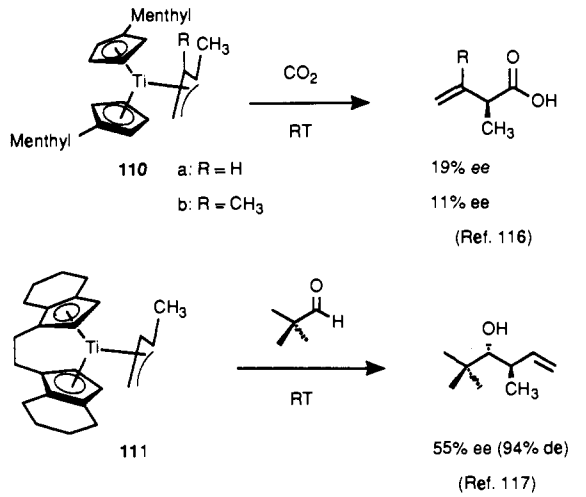
**Scheme 25**




4 (Scheme 4) 70 : 30 (40% de)

(Ref. 14)

**Scheme 26**




maximal diastereoselectivity of 7:3 is obtained with acetaldehyde[14] (Scheme 25). This result is actually very impressive, if the rather low dissymmetry of 4 is taken into consideration. Unfortunately, however, the transmetalation step is not stereoselective and the optical purity of the titanium center is partially lost. The enantiomeric purity of the product after cleavage from titanium is therefore considerably lower than the diastereomeric ratio in relation to the titanium center.

Trivalent titanocenes with $\eta^3$-bound allyl substituents are somewhat more reactive than the Ti(IV) analogs. An early example of a chirally modified reagent is the bis(menthylcyclopentadienyl) complex **110**.[116] Reaction with $CO_2$ at RT gives (*S*)-configurated $\beta,\gamma$-unsaturated $\alpha$-methyl carboxylates of low enantiomeric excess (Scheme 26. More promising are chiral ansa-bridged titanocenes, and excellent diastereocontrol (anti-preference) is achieved with the crotyl derivative **111**. The enantioface discrimination is, however, unexpectedly low, reaching a maximum of 55% ee for the transformation of pivalaldehyde (Scheme 26).[117]

## B. Enantioselective Aldol Reaction with Titanium Enolates

### 1. Stereocontrol by Internal Chiral Auxiliaries

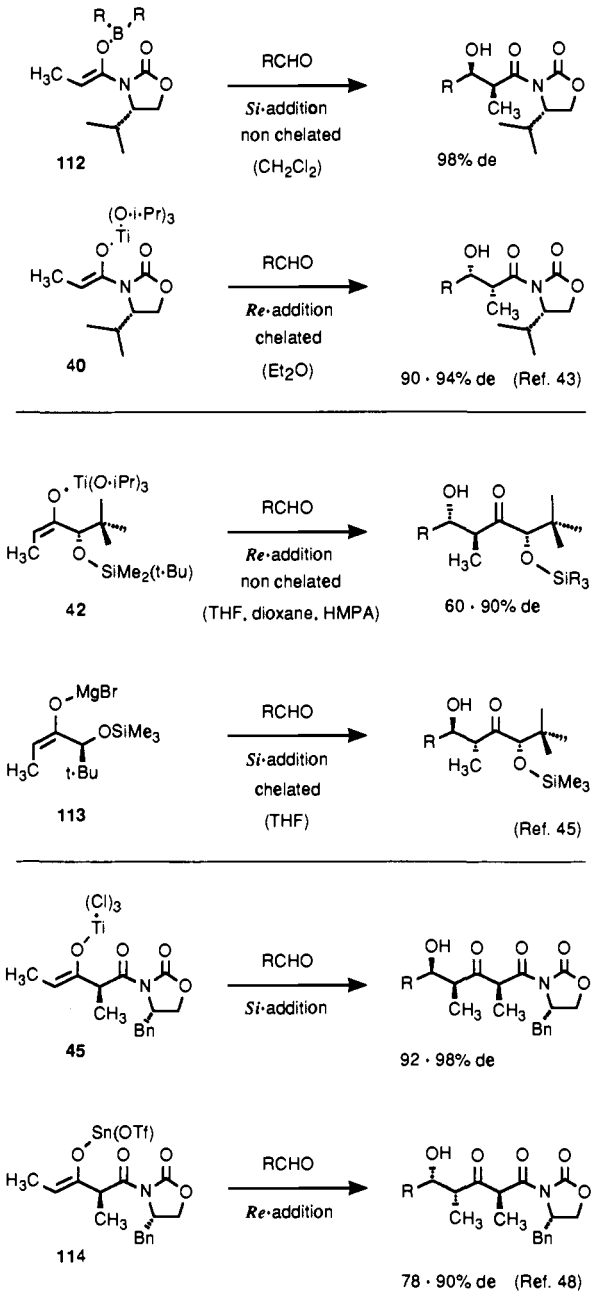
The aldol reaction has been developed into one of the most useful synthetic methods, as the stereoselectivity of the formation of two new asymmetric centers can be controlled with high predictability and selectivity.[102c,118] In contrast to the closely related allyl nucleophiles, the enantioface differentiation by enolates can be conveniently directed by internal auxiliaries, which are covalently bound as ester or amide derivatives. This "first generation" approach has several advantages. Isomerically pure compounds can be obtained even from reactions of moderate stereodifferentiation, as the diastereomeric products can often be separated. The sometimes cumbersome extra steps needed to introduce and remove these auxiliaries are, however, an inherent handicap of this principle, and the "second generation" approach, which makes use of chiral enolate counterions is preferable, if the enantioselectivity is high (see next chapter). Most challenging is asymmetric induction by catalytic amounts of chiral auxiliary. First successful steps toward this "third generation" of stereoselective aldolizations have been achieved with the gold-catalyzed addition of isocyanoacetate to aldehydes[119] and by using chiral Lewis acids for the Mukaiyama reaction with silyl enolates.[69,120]

An additional pivotal role in controlling the stereoselectivity of aldol additions is played by the counterion. It influences the geometry of the six-center cyclic transition state sterically, via metal ligands, and electronically, via its Lewis acidity and number of vacant coordination sites. As shown in Scheme 27, titanium enolates have become very popular in this respect, not only for improving selectivity[121a,b] but also for inverting the face selectivity obtained with other enolates. Thornton and co-workers realized first that the *Si* face preference of the boron enolate **112**[118a] is changed to *Re* addition, when the $(i\text{-PrO})_3$Ti enolate **40** (Chart 7) is used.[43] This effect is due to the ability of titanium but not boron to remain chelated to the oxazolidinone carbonyl while coordinating the substrate. Interestingly, the closely related chlorotitanium enolate **44** (Chart 7) reacts via a nonchelated transition state, affording the same stereoisomer as **112**.[47,121c] It may well be that the amine hydrochloride formed during the preparation of **44** is bound to titanium and that chelation is therefore prevented. In case of the titanium enolate **42** chelation is impeded by the lower nucleophilicity of the siloxy group, the bulk of the $(t\text{-Bu})Me_2Si$ substituent, and by solvatation (THF, dioxane, HMPA), and opposed to the chelating magnesium enolate **113**, *Re* addition is observed with **42** (Scheme 27).[45] Analogous observations have been made with the (*Z*)-titanium enolate **41** (Chart 7).[44] The synthetic potential of such titanium enolates has been demonstrated by Evans and co-workers.[48] In case of enolate **45** titanium not only serves for the purpose of reverting the facial preference of the tin(II) enolate **114**, but enables, by its comparingly mild method of preparation, an efficient and regiocontrolled enolization of this sensitive substrate (Scheme 27).

### 2. Stereocontrol by Chiral Titanium Ligands

Titanium complexes with chiral ligands have emerged as excellent templates for the stereoselective addition of C nucleophiles to carbonyl compounds (cf. sections III and IVA). The use of such complexes for the chiral modification of enolates is therefore a promising approach to enantioselective aldol reactions. As opposed to the chiral auxiliary approach (see above) the chiral ligands are recovered easily upon hydrolytic workup, and no additional manipulations on the products are needed. Interesting diastereocontrol has been achieved with achiral titanium enolates. The syn diastereomers are formed preferentially, if no cyclopentadienyl ligands are involved.[122]

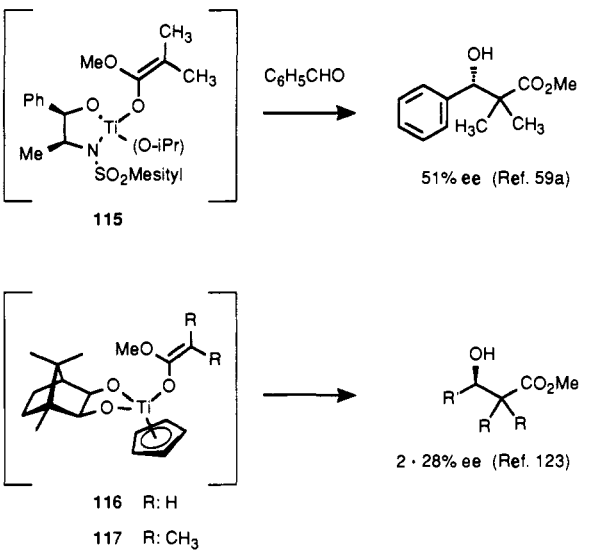
**Scheme 27**



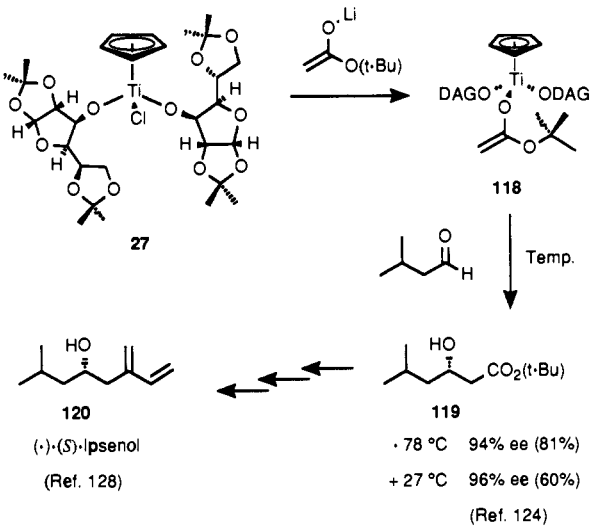

Early examples of titanium enolates with chiral ligands have been reported by Reetz and co-workers. The titanium enolate **115** with the norephedrine-sulfonate ligand, also used for enantioselective alkylations (cf. Chart 9, Table 4), induced 51% ee upon reaction with benzaldehyde (Scheme 28).[59a] Transmetalation of acetate and isobutyrate enolates with chloride **53** (Chart 9) gave the titanium reagents **116** and **117**. The low selectivity of aldol reactions is probably due to insufficient asymmetry of the camphanediol ligand (Scheme 28).[123]

Much better results were obtained, when the cyclopentadienyltitanium chloride **27** with diacetone glucose ligands (Chart 6)[36] was used for aldol reactions. Transmetalation of the Li enolate of *tert*-butyl acetate affords the titanium enolate **118**, which adds with high *Re*-face preference to various saturated, unsaturated, and aromatic aldehydes (Scheme 29).[124] The enantiomeric excess ranges from 90% to 96% ee and is essentially

**Scheme 28**




**Scheme 29**




independent of the reaction temperature. Addition to isovaleraldehyde yields **119** with 95 ± 1% ee in a temperature range of −74 °C to +27 °C. Reagent **118** is at the moment the most useful chiral acetate enolate known. Diacetone glucose is one of the most readily available chiral auxiliaries, and enantioselectivities surpassing the results of most other methods[69,120d,g,125] can be obtained at room temperature. Comparable induction has so far only been obtained with the rather sophisticated 2,4-dialkylborolanes introduced by Masamune[126] and Reetz.[127] Aldolate **119**, prepared on a 2 mol scale, has been converted to (−)-(*S*)-ipsenol (**120**),[128] the aggregation pheromone of various species of bark beetles.

A clear drawback of reagent **118** is that the enantiomer is not readily available, as no practical source or easy access to L-glucose exists. In the case of the allyltitanation an alternative is offered by complex **99** derived from (*R,R*)-tartrate. The *Si*-face selectivity of this reagent turned out to be even higher than the induction with the diacetone glucose complex **98** (Scheme 22). Chloride **49** (Scheme 10)[38,39] was therefore used for the transmetalation of acetate enolates. As expected, the corresponding reagent **129** showed *Si*-face preference, but the enantioselectivity was disap-

**Scheme 30**

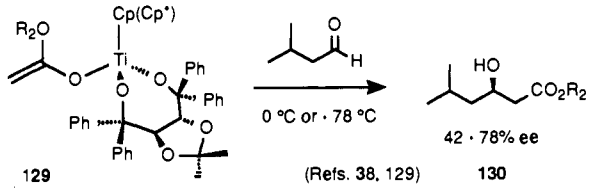


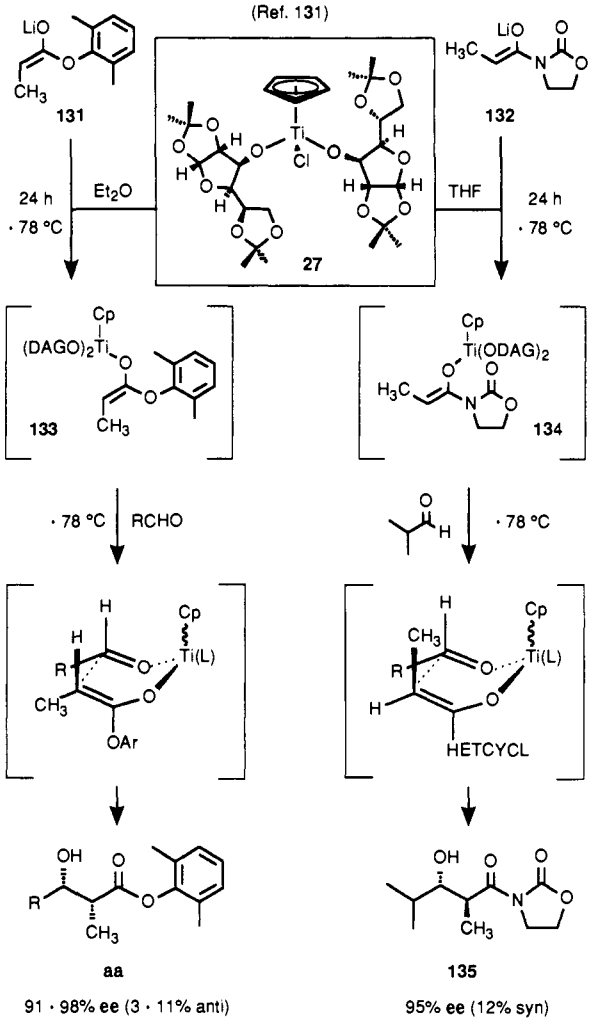

**Table 9. Enantioselective Acetate Aldol Reaction, Using Various (*R,R*)-Tartrate-Derived Titanium Ligands (Cf. Scheme 30, refs 38 and 129)**

| reagent 129 | | ester: | | enantiomeric |
|---|---|---|---|---|
| $R_1$ | Cp (Cp*) | $R_2$ | *T*, °C | excess (130), % |
| phenyl | Cp | methyl | -78 | 62 |
| phenyl | Cp | *tert*-butyl | -78 | 78 |
| | | | 0 | 54 |
| phenyl | Cp | 2,6-di-*tert*-butyl-4-methylphenyl | -78 | 74 |
| methyl | Cp | *tert*-butyl | -78 | 42 |
| methyl | Cp* | *tert*-butyl | -78 | 57 |

pointing (Scheme 30). The optical purity of the isovaleraldehyde adduct **130**, obtained by varying the substituents of the titanium ligands, the ester group, and the reaction temperature is listed in Table 9.[38,128] In contrast to **118** a normal temperature dependence of the enantiomer ratio is found. Bulky ester groups give rise to better results, but the maximal enantiomeric excess obtained with *tert*-butyl acetate (78% ee) could not be surpassed with larger groups. In analogy to the allyl transfer, the induction is reduced, when the phenyl substituents of the ligand are replaced by methyl groups and again increased by the introduction of a pentamethylcyclopentadienyl (Cp*) substituent, but both effects are less pronounced. So far no useful ligand for the *Si*-face addition of acetate enolates could be found.

In the case of substituted enolates reacting via cyclic transition states, the double bond geometry, *E* or *Z*, is directly related to the relative configuration, syn or anti, of the aldol products.[8,118] Therefore, the isomerically homogeneous Li enolates **131**[130] and **132** were used for the transmetalation with the chiral titanium chloride **27**, affording the (*E*)-titanium enolate **133** and the (*Z*)-amide–enolate **134** (Scheme 31). At −78 °C the lithium–titanium exchange is rather slow (24 h), but as opposed to transmetalation with $(i\text{-PrO})_3\text{TiCl}$, where 2–4 equiv are needed to quench reactions from Li enolates,[43,44] only a slight excess of **27** (1.1–1.2 equiv/Li) suffices for complete suppression of the Li pathway. Reaction of **133** with various aldehydes yields *syn*-aldols **aa** with high diastereoselectivity and *Re*-face selectivity (Scheme 31, Table 10).[131] As shown in Scheme 31 a "boat" conformation of the transition state has to be assumed, to explain the diastereocontrol. This is not unusual, and *syn*-aldols from (*E*)-enolates have been obtained with enol borates,[132] titanium,[122], as well as with zirconium, and other transition metal enolates.[133] Astonishing is, however, that reaction of the (*Z*)-enolate **134** with isobutyraldehyde gives the anti diastereomer **135**.[131] At the time, this was the first case, where aldolization of a (*Z*)-enolate has been associated with a "boat" transition state. For two other anti-selective aldol reactions, one involving a titanocene enolate[134] the other the recently reported zirconocene enolate **43**[46] (cf. Chart 7), "boat" transition states can be suspected.

**Scheme 31**




After the appearance of the results with **27**,[131] Myers and Widdowson submitted a paper describing an anti-selective aldol reaction with a "boat" transition state.[135]

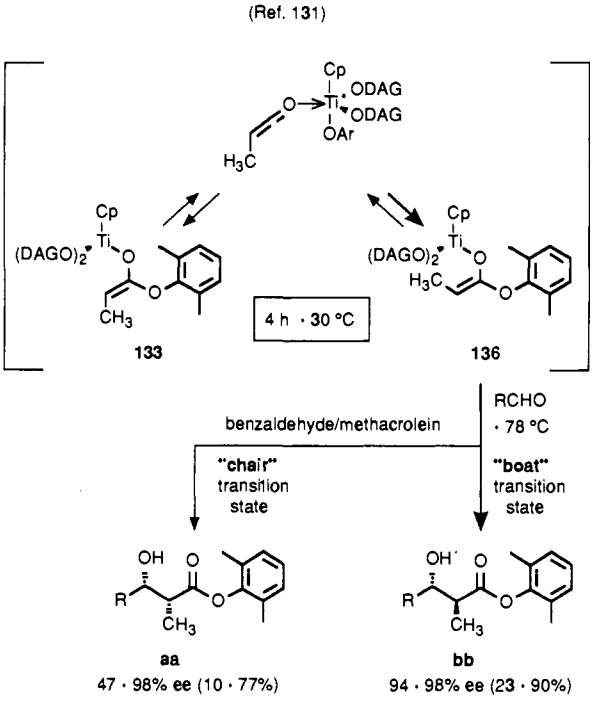
Despite the interesting stereoselectivity obtained with enolate **134**, this reagent is of limited practicability, due to low solubility and side reactions of the primary product, the Ti aldolate.[131] It was, however, discovered by serendipity, that the (*E*)-enolate **133** can be equilibrated at −30 °C to the thermodynamically more stable (*Z*)-enolate **136**, most probably via a titanium-bound ketene intermediate (Scheme 32).[131] Such a mechanism is reasonable, since ketene intermediates account for the thermal decomposition of the sensitive enolates **131** and **133** and since titanium enolates have been prepared from ketenes and titanium alkoxides.[136] Reaction of (*Z*)-enolate **136** with various aldehydes affords *anti*-aldols **bb** of high enantiomeric purity via a "boat" transition state. Exceptions are benzaldehyde[90] and methacrolein, which yield larger amounts of syn epimers **aa** of lower optical purity. It seems, that in the case of enolate **136** a "chair" transition state competes with the favored "boat" transition state (Scheme 32).[131] The results of the aldol additions of enolates **133** and **136** are compiled in Table 10. It is evident that this is one of the most powerful and practicable methods for the preparation of propionate aldols: the same derivative can afford either syn or anti diastereomers, according to the reaction conditions; a cheap noncovalently bound "external" auxiliary

**Table 10. Aldol Reactions with the Propionate Enolates 133 and 136 (Schemes 31 and 32, ref 131)**

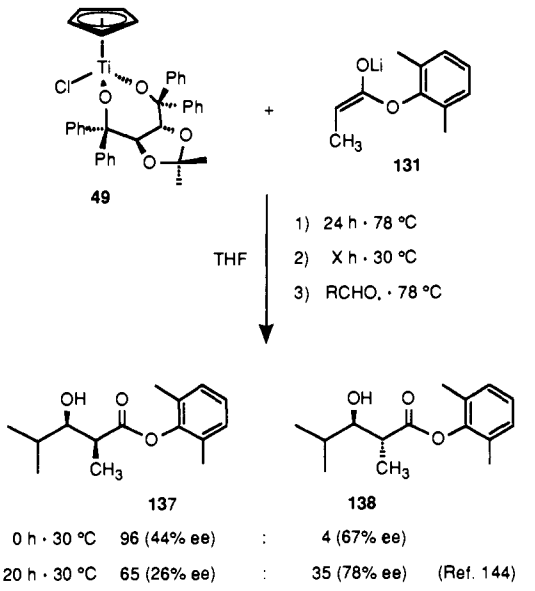
| | | *syn*-aldol **aa** | | *anti*-aldol **bb** | | |
|---|---|---|---|---|---|---|
| aldehyde | reagent | relative amount, % | enantiomeric excess, % | relative amount, % | enantiomeric excess, % | total yield, % |
| butanal | **133** | 92 | 95 | 8 | *a* | 87 |
| | **136**[b] | 11 | 98 | 89 | 95 | 74 |
| isobutyraldehyde | **133** | 94 | 97 | 6 | *a* | 76 |
| | **136**[b] | 10 | *a* | 90 | 96 | 76 |
| pivalaldehyde[c] | **133** | 89 | 91 | 11 | *a* | 71 |
| | **136**[b] | 17 | 72 | 83 | 98 | 59 |
| acrolein | **133** | 97 | 96 | 3 | *a* | 79 |
| | **136**[b] | 19 | 66 | 81 | 98 | 61 |
| methacrolein | **133** | 96 | 93 | 4 | *a* | 61 |
| | **136**[b] | 46 | 55 | 54 | 94 | 50 |
| benzaldehyde | **133** | 96 | 94 | 4 | *a* | 82 |
| | **136**[b] | 77 | 47 | 23 | 94 | 73 |

[a] The optical purity of the minor isomer has not been determined. [b] Mixture of enolates after equilibration of **131** for 4 h at −30 °C. [c] Reaction temperature −50 °C for **131** and −30 °C for **136**.

**Scheme 32**




**Scheme 33**

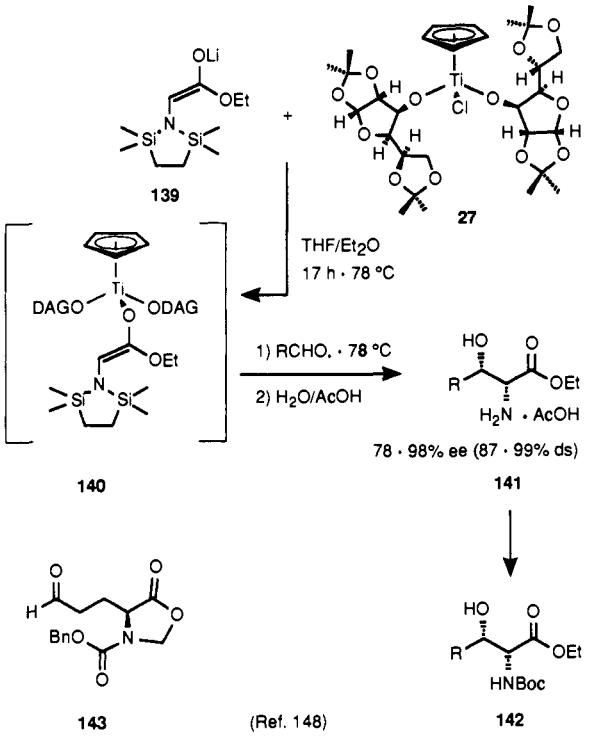



induces high optical purity; the products, aryl esters **aa** and **bb**, are versatile synthetic intermediates. Competing alternatives for the preparation of *syn*-aldols based on "external" auxiliaries are chiral boron[125f,137] or tin enolates[138] and especially catalytic variants of the Mukaiyama reaction.[120] Optically pure *anti*-aldols are less readily available, and most methods still rely on covalently attached chiral auxiliaries. With a few exceptions,[45,135,139] Lewis acid catalysis is needed for anti selectivity.[125d,e,140] With the exception of a Li enolate complexed by a chiral base,[141] only rather exotic chiral boron enolates of bulky thiol esters[126,127c,142] have so far yielded *anti*-aldols by "external" auxiliary control.[143] These methods can therefore not compete in cases, where the titanium enolate **136** can be applied successfully.

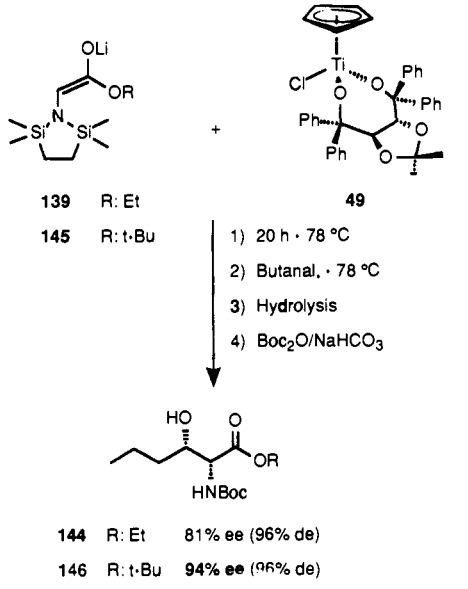
Unfortunately, the titanium enolates derived from chloride **49** react again less selectively than **133** and **136** (Scheme 33).[144] The enantiomers of **aa** and **bb** are therefore not readily available by this methodology. After transmetalation of Li enolate **131** with the titanium complex **49** at −78 °C, the *syn*-aldol **137** is obtained with high diastereoselectivity (92% de) upon reaction with isoburyraldehyde, thus confirming complete lithium–titanium exchange. The titanium ligand derived from (*R,R*)-tartrate induced, as expected, *Si*-face preference, but the optical purity of **137** is low (44% ee). The syn/anti ratio can also be affected by warming to −30 °C after transmetalation. The enolate equilibration is, however, much slower than in the case of **133**, and the ratio of the diastereomeric products **137** and **138** reaches only 65:35, still in favor of the syn epimer **137**. The enantiomeric excess of the minor anti product **138** is higher (78% ee). Without structural data of the titanium enolates, it cannot be said, whether this result is due to incomplete enolate isomerization, or, more probably, to unselective reaction of the (*Z*)-enolate ("boat" and "chair" transition states). Similar observations were made with the achiral enolate derived from cyclopentadienyldiisopropoxytitanium chloride.[131]

Aldol reactions of glycine enolates or equivalents[145] lead to β-hydroxy α-amino acids, important synthetic targets, as β-hydroxylated derivatives of many proteinogenic and nonproteinogenic amino acids are found in biologically interesting peptides of microbial origin. Transmetalation of Li enolate **139**[146] derived from the "stabase"-protected glycine ethyl ester[147] with titanium complex **27** gives the chiral titanium enolate **140**, which

**Scheme 34**




**Scheme 35**




is again a highly stereoselective reagent. Addition to various aldehydes and mild acidic hydrolysis gives (*R*) configurated *threo*-β-hydroxy α-amino acid ethyl esters **141** of very high diastereomeric and enantiomeric purity (Scheme 34).[148] As opposed to other methods, where deprotection is often a major problem, the esters **141** are versatile intermediates. Acidic hydrolysis gives the free amino acids, or else any N protection, e.g. the *tert*-butyl carbamate of **142**, can be introduced by standard methods. The titanium enolate **140** is a very mild reagent, and sensitive substrates like the glutamate semialdehyde **143** can be used for aldolization.[148] The stereoselectivity of this stoichiometric process is generally higher than diastereo- and enantioselectivity of the gold-catalyzed addition of isocyanoacetate to aldehydes,[119] the only competitive method.

(*S*) configured *threo*-β-hydroxy α-amino acids can be obtained by transmetalation of the Li enolate **139** with the chiral titanium complex **49** (Scheme 35).[149] The optical purity of the product **144** is again considerably lower (81% ee), when compared to the 98% ee obtained with the diacetone glucose reagent **140** for the same substrate. In this case, however, excellent stereoselectivity can be obtained by using the Li enolate **145** of the analogous glycine *tert*-butyl ester derivative (**146**, 94% ee).

## V. Abbreviations

| | |
|---|---|
| Cp | cyclopentadienyl ($C_5H_5$) |
| Cp* | 1,2,3,4,5-pentamethylcyclopentadienyl ($C_5Me_5$) |
| $d^1$-nucleophile | nucleophilic Ti ligand reacting at atom 1[5c,d] |
| $d^3$-nucleophile | nucleophilic Ti ligand reacting at atom 3[5c,d] |
| DAGO | 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl |
| HMPA | *N,N',N''*-hexamethylphosphotriamide |
| M | atom of a metallic element |
| RT | room temperature (ambient temperature) |
| salen | 1,2-bis-[[(2'-hydroxyphenyl)methylene]amino]ethane |
| THF | tetrahydrofuran |
| TMEDA | *N,N,N',N'*-tetramethylethylenediamine |

## Notes Added in Proof

According to Höhlein and Schobert (Höhlein, U.; Schobert, R. *J. Organomet. Chem.* **1992**, *424*, 301–306) one cyclopentadienyl ligand of $Cp_2TiCl_2$ can be substituted by an alkoxide ligand upon treatment with an alcohol and triethylamine. The cyclic complex **49** (Scheme 10) has been prepared by this method.

Another example of a indenyl ligand with a chiral substituent (3α-chlolestanyl) had been prepared and used for a zirconocene polymerization catalyst (cf. section II.C.1, Charts 4 and 5). (Erker, G.; Temme, B. *J. Am. Chem. Soc.* **1992**, *114*, 4004-4006.)

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