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Asymmetric C–C-bond formation with titanium carbohydrate complexes

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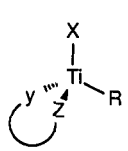
Abstract: - A novel class of titanium complexes, cyclopentadienyl-dialkoxy-chlorotitanates, is described. Two chiral representatives **4** and **8**, the former with two diacetone-glucose ligands, the latter with the bidentate (2*R*,3*R*)-2:3-isopropylidene-1,1,4,4,-tetraphenyl-threitol ligand, give highly enantioselective reagents, if the chloride is substituted by a transferable group. Allyl-groups and ester-enolates are thus added to various aldehydes, affording homoallyl-alcohols, acetate and propionate aldols, as well as β-hydroxy-α-aminoacids of high optical purity, generally 90 - 98% ee. Reagents derived from **4** attack the *re*-side, those derived from **8** the *si*-side of aldehydes. With several α-chiral substrates almost complete diastereocontrol is achieved in allylations of the threitol-derived reagents. The complexes **4** and **8** have been analysed by X-ray-diffraction, ^{1}H- and ^{13}C-NMR. Molecular modelling has been used to analyse the conformation of **4**, and to estimate the strain of dioxa-titanacycles of various ring size.

INTRODUCTION

New materials based on chirality (*e.g.* ferroelectrics), and the inevitability of enantiomerically pure compounds for specific interactions with biological systems challenge the development of improved methods for "asymmetric synthesis". Major trends include partial synthesis from readily available natural products, enantioselective processes catalyzed by enzymes, efficient methods for the resolution of racemates, and reactions, stoichiometric and catalytic, mediated by chiral transition metal complexes. None of these methods will, however, offer at any time a general solution. Some like enzyme catalysis are best suited for the large scale production of specific compounds, others allow an expedient and predictable access to target compounds, but on a limited scale. Despite of the enormous amount of work published in this field, there is a remarkable deficiency of practicable methods for an intermediate scale (5g - 100g), especially concerning the most demanding class of enantioselective processes, the C-C-bond forming reactions. For these resons we embarked in a project on chiral organo-titanium- and organo-zirconium-reagents. Such complexes are readily available, offer interesting reactivity, and, so far, no intrinsic toxicity could be related to these elements (refs. 1,2).



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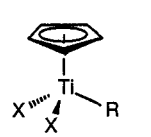

X, Y, Z: R'O, R'$_2$N

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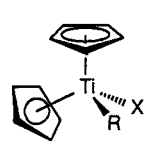

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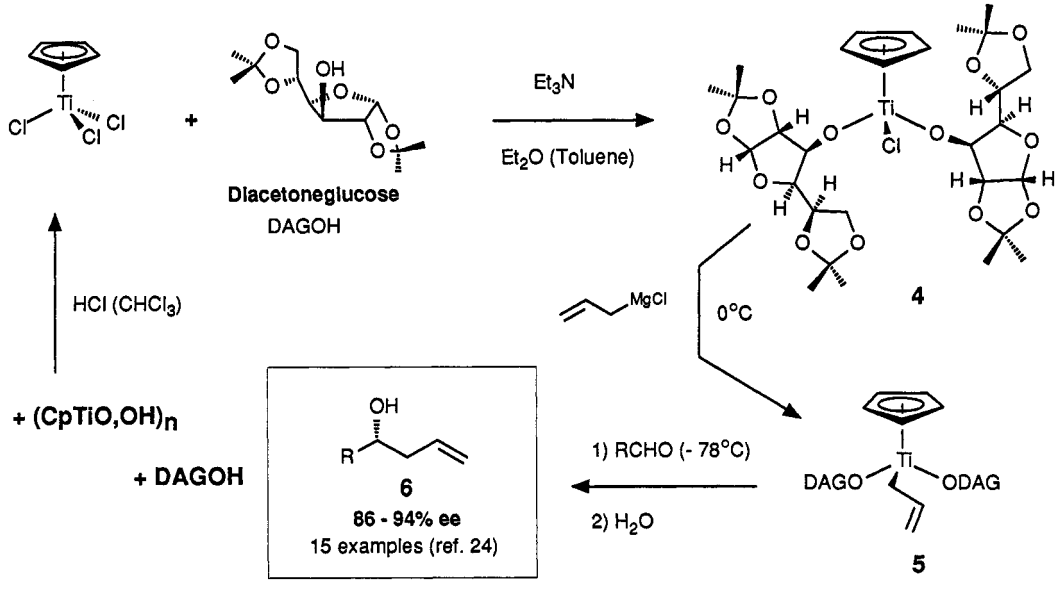
Crucial for a success is the proper choice of complex and chiral ligand. To meet the requirements of a stereoselectivity inducing template, such reagents should be stable, chemically and geometrically defined species. In complexes of type **1** the stabilisation by the alkoxy or amido substituents is still inadequate, even with bidentate ligands, and their use for transfering carbon nucleophiles enantioselectively to aldehydes is limited to a few successful examples (refs. 3-6). More promising is, however, their use as chiral *Lewis*-acids in cycloadditions (ref. 7) or *ene*-reactions (ref. 8). Therefore we concentrated our efforts on complexes of type **2** or **3**, where one or two of the 2-4 electron donating ligands (X,Y,Z) is replaced by a six electron donating cyclopentadienyl ligand. The electronic and steric stabilisation thus obtained should allow the use of readily available, cheap monodentate alkoxy or amido ligands as chiral auxiliaries. Two of the substituent in **2** or **3** should be identical, to avoid that titanium becomes a stereogenic center.

ADDITION OF ALLYL GROUPS TO ALDEHYDES

Although the ultimate goal of this project is the stereocontrolled transfer of any carbon nucleophile from titanium to various oxygen and nitrogen electrophiles, we chose the addition of allylic groups to aldehydes as a starting point for different reasons: in contrary to the alkyl transfer this is a well understood process and in most cases a "monomeric" bimolecular cyclic transition state can be assumed. Furthermore the resulting homoallyl-alcohols containing one or two additional stereogenic centers are valuable synthetic intermediates (ref. 9). It is therefore not surprising that powerful enantioselective allyl-transfer reagents have been developed, the most impressive being allyl-boron derivatives (refs. 10-14). With the exception of the highly stereocontrolled addition of chiral allyl-groups (refs. 15,16), however, no really successful allyl-titanium reagent with chiral ligands has so far been reported (refs. 17-19). This is astonishing, since high diastereocontrol has been observed for achiral allyl-titanates (refs. 20-22).

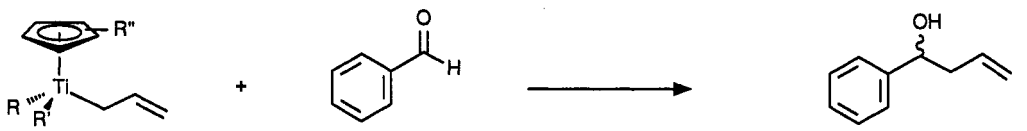
With this premise we prepared the complex **4** from $CpTiCl_3$ and diacetone-glucose (*Scheme 1*). The best results are obtained in Et_2O or toluene as solvent, the HCl evolved being neutralized with a slight excess of Et_3N. Deprotonation of the auxiliary with BuLi or NaH turned out to be less suited for the preparation of **4**. Complex **4** can be isolated under exclusion of moisture and is fully characterized (see below, Analyses and Calculations), but storage as a stock solution of estimated content is recommended. The remaining chlorine-ligand of **4** can then be substituted for groups, which are transferable to electrophiles (Note a:). Thus metathesis with allylmagnesium chloride gives the allyl-titanate **5**, $MgCl_2$ being precipitated, and reaction with aldehydes at -78°C affords homoallylalcohols **6** with good yield (50 - 88%) and excellent enantioselectivity (86 - 94% ee, addition to the *re*-side of RCHO). Upon aqueous workup both the chiral inductor and the Cp-titanium complex, in the form $(CpTiO,OH)_n$, can be recovered and recycled to **4** (*Scheme 1*, ref. 23).

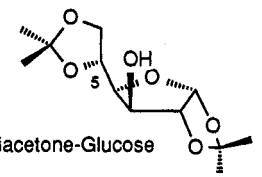
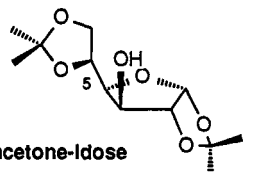
Scheme 1



Note a: The preparation of complex **4**, its analysis and use for enantioselective transformations have been described recently by us in communications (refs. 23-26).

Scheme 2



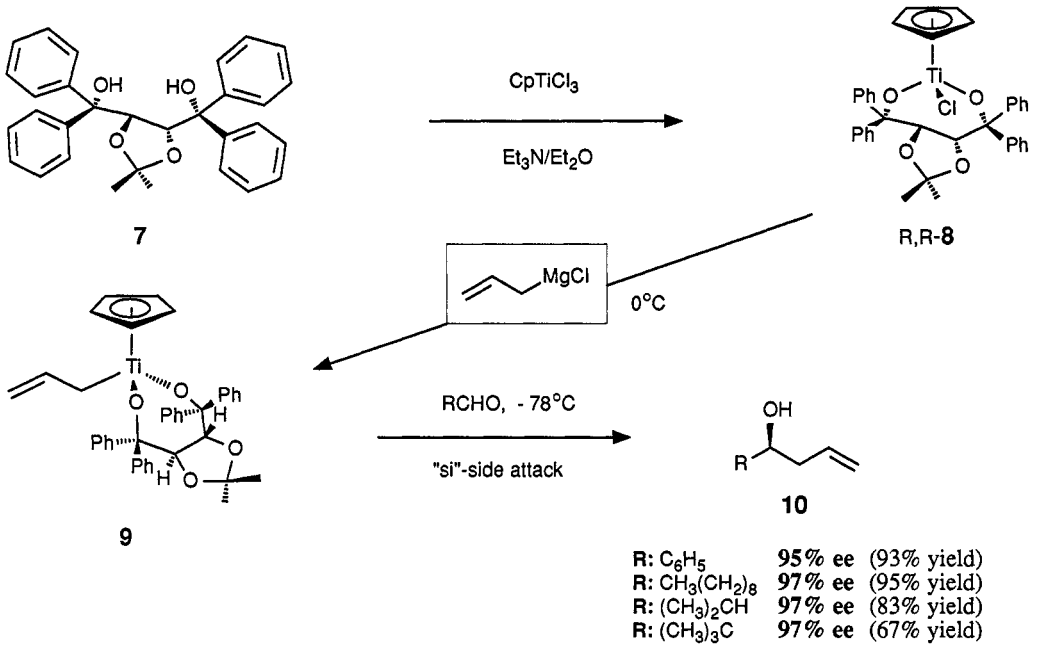
R, R':  Diacetone-Glucose	R": H, $SiMe_3$, pentamethyl	85 - 90% ee (*R*-Enantiomer)
R: Diacetoneglucose R': Cl	R": H	21% ee (*R*-Enantiomer)
R: Diacetoneglucose R': Allyl	R": H	47% ee (*R*-Enantiomer)
R, R':  Diacetone-Idose	R": $SiMe_3$	67% ee (*S*-Enantiomer)
	R": H	39% ee (*S*-Enantiomer)
	R": pentamethyl	30% ee (*R*-Enantiomer)

Lacking success with monodentate alkoxy ligands other than diacetone-glucose and related derivatives with different acetal protecting-groups, we turned our attention to bidentate auxiliaries, well aware of the danger, that the synthesis of cyclic titanium complexes might be difficult for thermodynamic or kinetic reasons (refs. 27,28). To our delight the threitol-derivative **7**, available in two steps from tartrate (both configurations, refs. 1,3), turned out to be another lucky strike. With diol **7**, derived from natural *R,R*-(+)-tartaric acid, the extraordinarily stable titanacycle *R,R*-**8** is obtained without any problem by the same method as used before. The corresponding allyl-reagent *R,R*-**9** adds now to the *si*-side of aldehydes, thereby affording products **10** of opposite configuration with excellent yield and enantioselectivity (*Scheme 3*).

Both systems, the *bis*-diacetoneglucose complex **4** (ref. 23) and the threitol-chelate **8**, can be used for the transfer of substituted allyl-groups. As illustrated in *Scheme 4*, *anti*-products **11** are obtained exclusively, irrespective of the geometry of the organometallic species used for the preparation of allyl-titanates **12**. This is due to a fast equilibration of the η^1-bound allyl-titanates to the most stable *trans*-isomer with titanium bound to the less substituted carbon (see below, Analyses and Calculations). This might as well be the reason, that we were so far unable to prepare homoenolate-reagents in analogy to the work of *Hoppe* (ref. 16) and *Helmchen* (ref. 15).

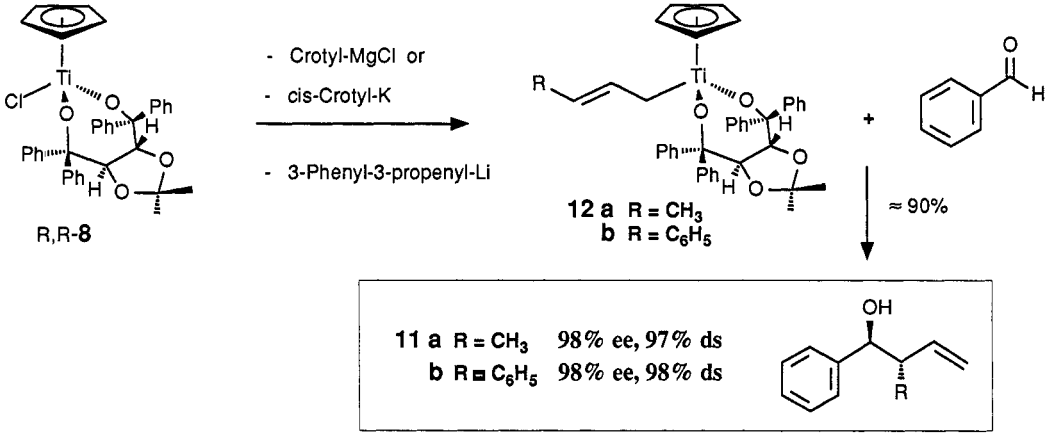
To gain more insight in the reactivity and stereoselectivity of these novel complexes, some allyl-titanates related to **5** have been prepared and tested by their reaction with benzaldehyde (*Scheme 2*). Not much change is observed upon replacement of the cyclopentadienyl ligand with $SiMe_3$-Cp or pentamethyl-Cp(Cp*), but the enantioselectivity is lost, when one of the diacetoneglucose substituents is replaced by chlorine or another allyl-group. With the aim of discovering another auxiliary, which might induce the opposite *si*-face selectivity, several carbohydrate derivatives were tested without success. An illustrative example for the stringent structural requirements of such a ligand is diacetone-idose, which differs only in the configuration of C(5) from diacetone-glucose, a seemingly unimportant change. The idose-complex corresponding to **4** is, however, much more labile, and so far isolation and characterisation by NMR has been precluded by its instability. May be as a consequence of this the allylated derivative is much less stereoselective (39% ee), and to our astonishment induces the opposite chirality (*si*-face addition). Replacement of Cp by $SiMe_3$-CP results in better induction (67% ee) probably by reinforcement of the R*O-Ti-bonds. With Cp*, on the other hand, the other enantiomer is formed (30% ee, *Scheme 2*).

Scheme 3



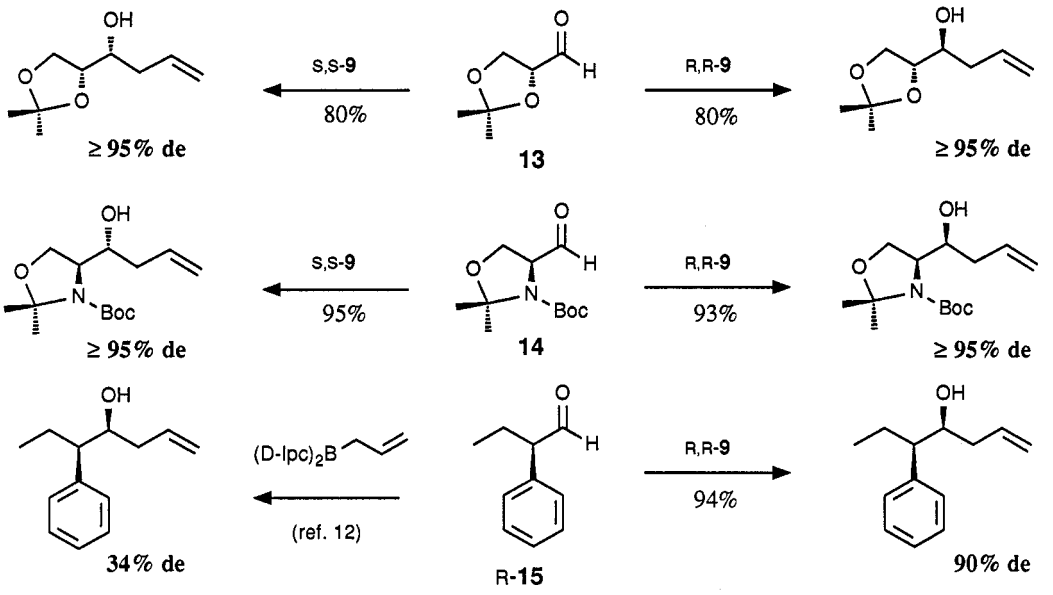
Thus, in contrary to allyl-boron reagents (refs. 10-14), *syn*-crotyl adducts are not accessible by our method. A similar *anti*-preference has been reported before for other crotyl-titanium compounds (refs. 19-22). An interesting reversal to *syn*-selectivity has, however, been observed by *Reetz* (ref. 21), when $BF_3{\cdot}Et_2O$ was added to the aldehyde prior to the reaction with a crotyl-titanocene complex.

Scheme 4



In *Scheme 5*, finally some examples of allyl-addition to α-chiral aldehydes are given. In the case of *D*-glyceraldehyde **13** and *Garners L*-serinal-derivative **14** (ref. 29) the degree of reagent control approaches the accuracy of the product analysis by capillary-GLC (Chirasil-Val^R, ref. 30), limited here by the optical purity of the starting materials (96 - 98% ee). An experiment with an achiral analogon of **9** would be needed to identify the mismatched pairs. A final "crash-test" was then made with 2-phenyl-butanal **15**, the worst example (34% de) reported for allylations with *Brown's* di-isopinocamphenyl-allyl-borane (ref. 12). Sure enough, a mismatched pair could now be identified, and a 95 : 5 isomer ratio (90% de) was obtained from the reaction of *R*-**15** with *R,R*-**9**. For the matched case, *S*-**15** and *R,R*-**9**, the diastereomeric excess exceeded 98%. Reaction of **15** with the *bis*-diacetone-glucose reagent **5** gave inferior results, with 98% de for the matched and 59% de for the mismatched pair. It can therefore be stated, that the threitol reagents available in both configurations, *R,R*-**9** and *S,S*-**9**, transfer allyl-groups with higher stereoselectivity to aldehydes than the *bis*-diacetoneglucose reagent **5**.

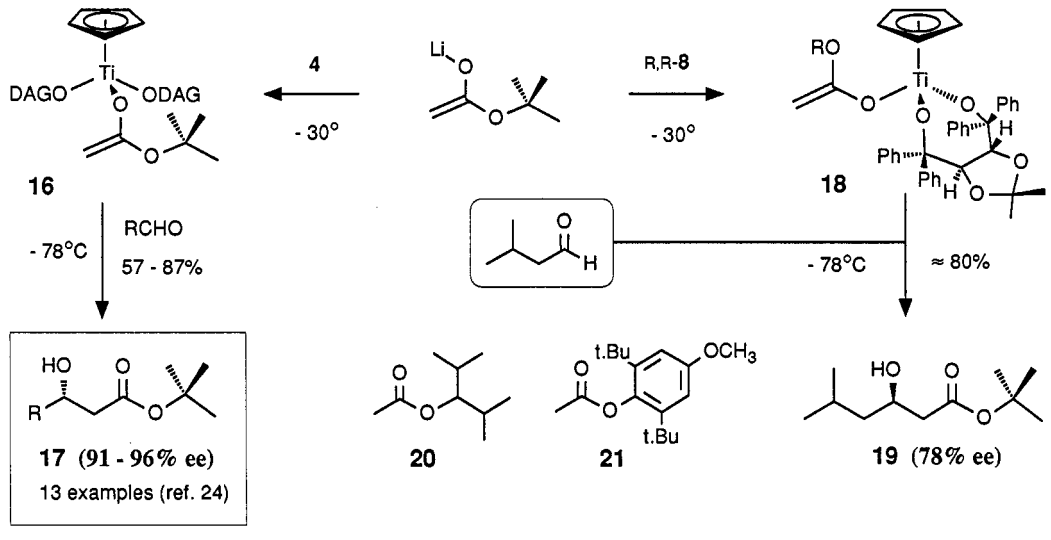
Scheme 5



ALDOL REACTIONS

As the aldol-reaction, one of the most useful C-C-bond forming processes (ref. 31), is related in mechanism to the transfer of allyl-groups, we applied our novel titanium complexes to this reaction as well. One of the long standing problems in this field is the stereocontrolled addition of acetyl-groups; expedient methods have appeared only recently (refs. 32-36). When the Li-enolate of tert.butyl acetate was treated at - 30°C with a toluene solution of the *bis*-diacetoneglucose complex **4**, the Ti-enolate **16** formed within a few hours. Reaction of **16** with various aldehydes at - 78°C gave the aldols **17** with excellent enantioselectivity (*re*-side addition) and good yields (*Scheme 6*, ref. 24). This result is especially valuable for α,β-unsaturated aldehydes, as these aldols can not be obtained by enantioselective hydrogenation of β-ketoesters (ref. 37).

Scheme 6

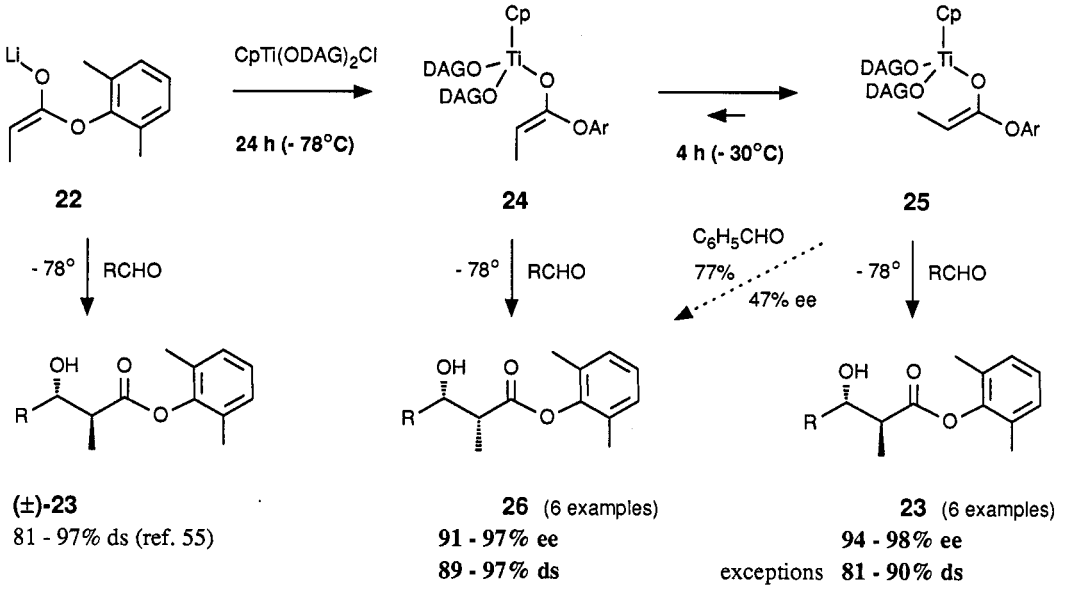


Unfortunately the corresponding enolate **18** derived from the threitol complex *R,R*-**8** is not nearly as selective as **16** and the optical purity of the enantiomeric aldol thus obtained is only 78%. The difference between the two systems is also evident from experiments at variable temperatures: while the stereoselectivity of **16**, tested with

isovaleraldehyde, appears to be unaffected by temperature changes (the fact that the optical purity of the product is 94±2% between -74 and +27°C can only be explained by a much higher intrinsic enantioselectivity of this process), the induction of enolate **18** drops from 78% ee to 54% ee, when the temperature is raised from - 78 to 0°C. In the case of **18** the enantioselectivity is also influenced by the size of the ester residue. With small esters a lower induction was observed: 63% ee for the ethyl ester and 62% ee for methyl acetate. The result with tert.butyl acetate (78% ee) could not be improved by larger groups: 70% ee with the (3-methyl-2-isopropyl)-butyl ester **20**, 74% ee with 2,6-di-tert.butyl-4-methoxyphenyl acetate **21**.

Since the pioneering work of *Reetz* and *Peter* (ref. 38) aldol reactions of propionyl-Ti-enolates have been described by several authors (refs. 39-47). With one exception (ref. 45) it appears, that, in analogy to Zr-enolates (refs. 48,49) and enol-borates (refs. 50,51), titanium-enolates lead to *syn*-aldols, irrelatively to the enolate-geometry. While moderate to excellent diastereofacial differentiation has been achieved with Ti-enolates of propionyl derivatives carrying chiral auxiliaries (refs. 43,44), no propionyl-enolates with chiral Ti-complexes have yet been reported. Chiral ligands have, on the other hand, turned out to be very effective in the case of borinyl- (refs. 33,34,52,53) and tin-enolates (ref. 54).

Scheme 7

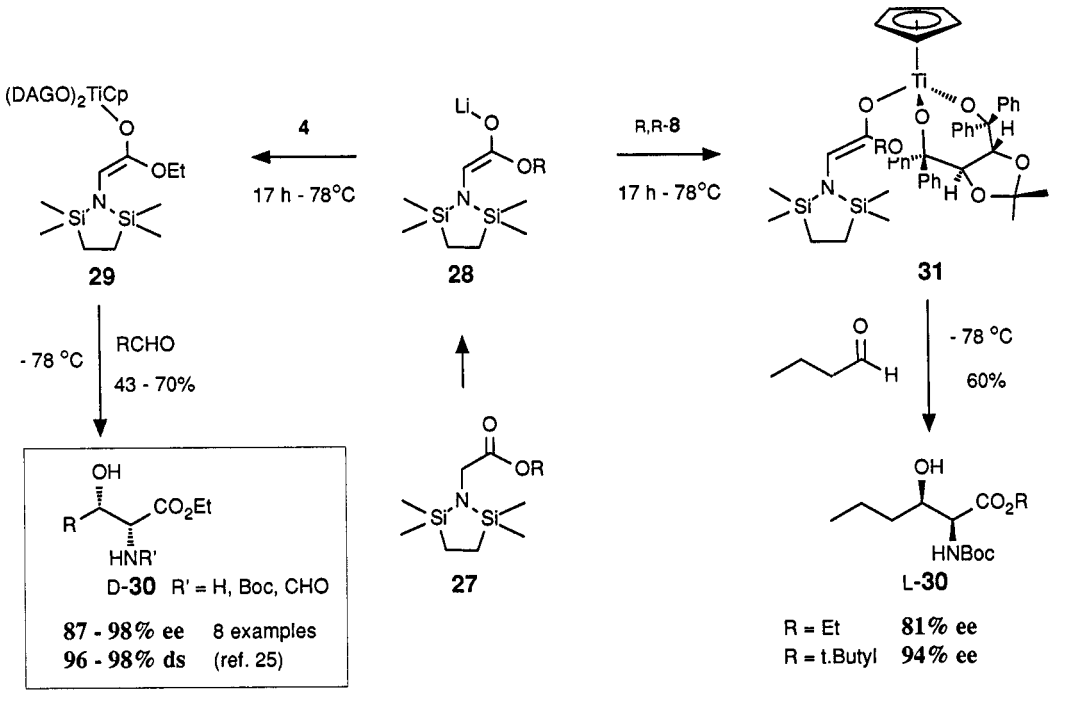


After several experiments with other propionyl derivatives, the Li-enolate **22** (ref. 55) turned out to be a suitable precursor for chiral titanium-enolates. Racemic *anti*-aldols (±)-**23** are obtained from **22** with a variety of aldehydes (ref. 55, *Scheme 7*). A considerable amount of experimentation was needed to find the optimal conditions for the transmetallation of **22**. With the *bis*-diacetoneglucose complex **4** 24 hours of reaction time are needed at -78°C, to obtain the *E*-configurated Ti-enolate **24**. At - 30°C this exchange would be much faster (1 - 2 h), but under these conditions the Li-enolate **22** is unstable, undergoing *Claisen*-condensation, probably *via* fragmentation to methylketene, and the *E*-enolate **24** is equilibrated to a thermodynamically more stable form, possibly the *Z*-isomer **25** (*Scheme 7*). The surprising result was, that *syn*-aldols **26** are formed with high stereoselectivity from *E*-enolate **24**, but *anti*-aldols **23** of equally high optical purity from the supposed *Z*-enolate **25**. Consistently with the other processes of the diacetoneglucose system, the *re*-side of the aldehydes is attacked by **24** and **25**. The diastereoselectivity of the *Z*-enolate **25** is somewhat lower than observed for the isomer **24**, and with certain aldehydes (benzaldehyde, methacrolein) large amounts of *syn*-isomer **26** are formed with low enantioselectivity, in addition to the *anti*-aldols **23** of high optical purity isolated from the same reaction mixtures. To date no experiments have been done with the threitol complex *R,R*-**8**.

These results comprise a valuable contribution to the aldol-methodology, as both epimers can be obtained in good optical purity from the same precursor, and especially, as only a few methods (refs. 33,52,53,56-59) give access to *anti*-aldols of high enantiomeric excess. From a mechanistic standpoint, these results could be explained by assuming six-membered transition states with twist-boat conformations for the reactions of both, the *E*-enolate **24** and the *Z*-enolate **25.** An alternative chair-like transition state of similar energy should then exist for those reactions of the *Z*-enolate **25**, where higher proportions of *syn*-aldols **26** are formed. It is interesting to note, that *anti*-adducts are obtained exclusively from the *trans*-crotyl titanate **12a** (*Scheme 4*). This implies a different chair-like transition state for the allyltransfer and could as well explain the different performance of the two chiral Ti-complexes **4** and **8** in these two processes: while the *bis*-diacetoneglucose complex **4** is better suited for aldol reactions, the threitol system *R,R*-**8** affords allylating reagents of higher stereoselectivity.

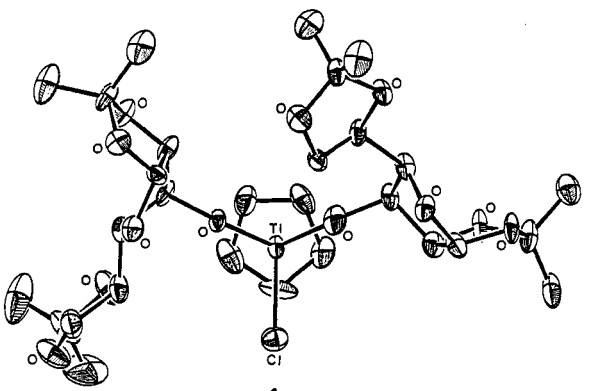
The development of new methods for the synthesis of enantiomerically pure α-aminoacids has become an important field of research (ref. 60). Therefore we decided to modify a glycine-enolate with our chiral titanium complexes. Because protecting-group manipulations are often a major problem in aminoacid chemistry, we chose the silyl-protected glycine ester **27** (ref. 61) as starting material. The corresponding Li-enolate **28** can be transmetallated with the *bis*-diacetoneglucose complex **4** at - 78°C (17 h), and the resulting titanium enolate **29** adds again to the *re*-side of various aldehydes, affording *threo*-β-hydroxy-α-aminoacid derivatives *D*-**30** of high optical purity (*Scheme 8,* ref. 25). Mild acid hydrolysis (AcOH) liberates the amine function, which can be derivatised with a suitable protecting group. The enantiomeric aminoacids *L*-**30** are obtained analogously by transmetallation with the threitol complex *R,R*-**8**. As observed before with the acetate enolate (*Scheme 6*) the threitol complex **31** is less stereoselective. In this case, however, the 81% ee of the ethyl ester can be raised to a satisfactory 94% ee by starting from tert.butyl glycinate. In contrary to the unselective Li-enolate **28**, both titanium-enolates **29** and **31** react with high diastereoselectivity to *syn(threo)*-products **30**. The result of the propionate aldolisation in mind, it is very likely, that the enolates **29** and **31** are *E*-configurated.

Scheme 8



ANALYSES AND CALCULATIONS

Crystals suited for X-ray diffraction could be obtained of both cyclopentadienyl-*bis*-alkoxy-chlorotitanates **4** (ref. 26) and **8** (Note b). *ORTEP*-drawings with vibration ellipsoids at the 20% probability level are illustrated below.



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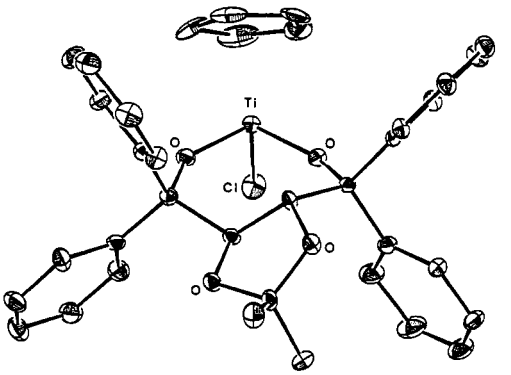

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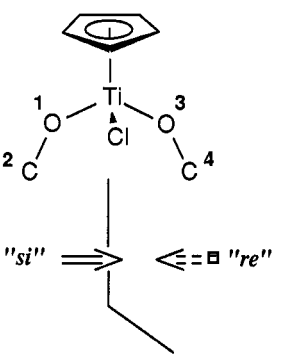
The complexes are monomeric and additional Ti-O interactions can be ruled out. To allow a comparison of the two species, selected structural data of the central $CpTi(O\text{-}C)_2Cl$-cores are given in the Table. According to the **Cp-Ti-Cl**-array, which defines a prochiral plane, one of the alkoxy ligands is attatched to the *si*-side, the other to the *re*-side of this plane (see illustration below). The coordination geometry is best described as a "three-legged piano-stool arrangement". Almost identical are the **Ti-Cp$_{center}$**-, **Ti-O**-bond lengths, the **O_1-Ti-O_3**-, and the **O-Ti-Cp$_{center}$**-bond angles of **4** and **8**.

TABLE: Selected bond lengths, bond angles, and torsion angles of **4** and **8**, numbers in parentheses are estimated standard deviations in the least significant digit.

		4	**8**
Bond lengths (nm)			
Ti - CP		201.3 (9)	207.0 (1.0)
Ti - O_1	*(si)*	180.9 (8)	178.3 (6)
Ti - O_3	*(re)*	178.6 (8)	178.8 (6)
Bond angles (°)			
O_1 - Ti - O_3		104.0 (4)	98.4 (3)
O_1 - Ti - Cp_{center}	*(si)*	117.0 (1.0)	120.0 (1.0)
O_3 - Ti - Cp_{center}	*(re)*	118.0 (1.0)	118.0 (1.0)
Ti - O_1 - C_2	*(si)*	145.8 (8)	155.2 (6)
Ti - O_3 - C_4	*(re)*	153.1 (9)	145.0 (6)
Torsion angles (°)			
Cl - Ti - O_1 - C_2	*(si)*	+ 115.0 (2.0)	- 124.6 (1.3)
Cl - Ti - O_3 - C_4	*(re)*	- 124.0 (2.0)	+ 103.0 (1.0)



Remarkably different are, however, the distortions due to the chiral ligands. The **Ti-O-C**-angles differ by 7 - 10° for the *re*- and the *si*-side. Interestingly the smaller angle (≈ 145°) is observed for the *si*-side of **4**, but for the *re*-side of *R,R*-**8**. One is now tempted to speculate, that this enantiomeric distortion is (partially) responsible for the chiral induction, which in fact is opposite for reagents derived from **4** (*re*-side attack) and **8** (*si*-side attack). Completely different are then the **Cl-Ti-O-C**-angles of **4** and **8** (opposite sign). While the **O-C(α)**-bonds of **4** are approximately eclipsed with the **Ti-Cp$_{center}$**-axis, the corresponding bonds of **8** are eclipsed with the opposite **Ti-O**-bond. The quarternary α-carbons of **8**, substituted with two phenyl-groups, and the constraints of the 7-membered ring preclude in this case the conformation of the diacetoneglucose ligands of **4**.

Note b: The crystal-structure analyses have been done by *Mrs. G. Rihs*, Ciba-Geigy AG, CH-4002 Basel (Switzerland). Part of the ^1H- and ^{13}C-NMR-spectra have been recorded by *Dr. U. Piantini*, University of Zürich CH-8057 Zürich (Switzerland).

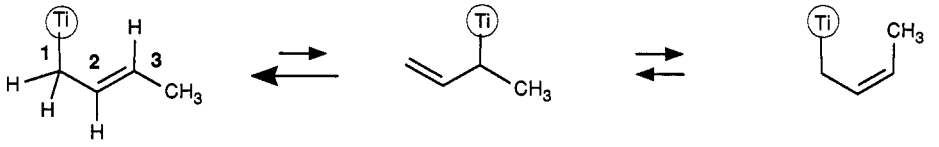
Despite all this structural information, the cause for the observed enantioselectivity of these reagents remains unknown. In addition to the fact, that the conformations in solution might be different from the crystalline state, a different spatial arrangement of the ligands is expected for the cyclic six-membered transition state with the extended coordination of titanium (additional bond to the aldehyde carbonyl-oxygen).

The main features of the ^{1}H- and ^{13}C-NMR-spectra are two sets of signals for the diastereotopic diacetone-glucose ligands of **4** and doubling of ligand-signals due to the loss of C_2-symmetry upon formation of complex **8**. The spectra of the flexible complex **4** have been analysed in more detail (ref. 26, Note b). A large complexation-shift (0.7 - 0.8 ppm), H-C(3) of diacetoneglucose, is observed in the ^{1}H-NMR. The ^{1}H- and the ^{13}C-NMR-spectra of **4** at 9.4 T are not affected by temperature: neither do the two ligand-signal sets collaps up to 100°C, nor do signals of other conformers appear, when the sample is cooled to - 100°C. This means, that ligand exchange or inversion of titanium is slow on the NMR time-scale, and that one conformer of **4** is favored. Due to overlapping signals, the torsion-angles C(4)-C(5) of diacetoneglucose in **4** could not be determined. Otherwise the coupling pattern was similar to the free ligand. Difference-NOE experiments revealed proximity of H-C(3) (both ligands) and of one of the 8 acetonide methyl-groups to the Cp-ligand. The corresponding distances of the X-ray sructure are 217 nm for H-C(3)^{si}-Cp, 233 nm for H-C(3)^{re}-Cp, and 243 nm for CH_3-Cp (*cf. Figure 2*, circled atoms and CH_3). It is therefore possible, that the stable conformation observed in solution corresponds to the crystal structure (see, however, below, MM2-calculations).

The allyl-titanium reagent **9** (*Scheme 3*) and **12a** (*Scheme 4*) were amenable to ^{1}H-NMR-analysis as well (*Figure 1*, ref. 26). The simple first-order non-dynamic spectrum of an η^1-bound *trans*-crotyl residue in the case of **12a** is deceptive, since fast 1,3-migration **and** *cis/trans*-isomerisation is observed down to - 100°C at 9.4 T (400 MHz) for the unsubstituted allyl-reagent **9**. Sustained by the experimental results of **12a** (see above, *Scheme 4*), one can therefore assume, that a strong thermodynamic preference of isomer **a** compared to **b** and **c** prevents the observation of dynamic effects in the NMR of the crotyl-titanate **12a**.

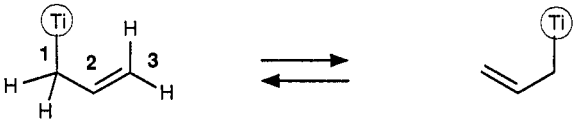
Figure 1

Compound 12a



2.26 and **2.17** ppm (*2dd*, J = 8.5, 8.5, **2H-C(1)**) **4.82** ppm (*dq*, J = 14, 6.5, **H-C(3)**)
5.46 ppm (*dtq*, J = 14, 8.5, 1.5, **H-C(2)**)

Compound 9



3.36 ppm (*d*, J = 11, **2H-C(1), 2H-C(3)**) **5.80** ppm (*quint.*, J = 11, **H-C(2)**)

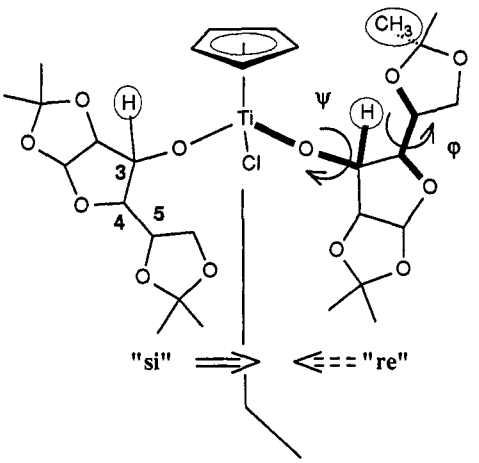
The NMR-analysis of the bis-diacetoneglucose complex **4** implicated a strong preference of one conformer, which could, however, not be determined (see above). We therefore decided to approach this problem by molecular modelling (Note c).

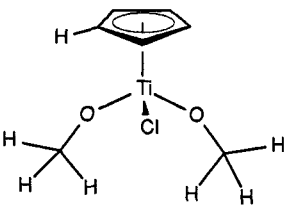
Note c: These calculations have been done by *Dr. H. Karfunkel* and *Dr. St. Bacci*, Ciba-Geigy AG, CH-4002 Basel (Switzerland).

As no parameters are available for such Ti-complexes, the X-ray geometry of the central $CpTi(O\text{-}C)_2Cl$-core was used as fixed entity. A quantum chemical *ab initio* computation was then done for the model compound $CpTi(OCH_3)_2Cl$, to get the atomic charges. The result using the GAMESS program (University of North Dakota) with STO-3g as the basis set and taking the atomic d-orbitals of Ti into account is shown in *Figure 2*. With these premises a conformational search was done, restricted to the torsion angles ψ and φ of each diacetoneglucose ligand. Applying the program MACROMODEL (version Columbia) with a cutoff energy of 20 kJ/Mol, 12 minimal-energy conformers were obtained, which roughly fall into three cathegories, exemplified by **#11**, **#3**, and **#1** (*Figure 2*). While ψ is not varying dramatically, the C(4)-C(5) torsion-angle φ is more interesting, and two very different values, + 75(±3)° or - 175(±3)°, seem to be preferred. The X-ray structure can be "relaxed", and corresponds therefore to an energy minimum with similar geometry as **#11**. While conformer **#1** is totally different, **#3** is most interesting. It is kind of a pseudo mirror-image of the X-ray conformer, as the *re*-ligand of **#3** assumes approximately the conformation of the *si*-ligand in the crystal and *vice versa*. The conformation of complex **4** in solution is therefore still uncertain. The NOE-effects observed in the ^{1}H-NMR could also be explained with conformer **#3**.

Figure 2

Compound 4





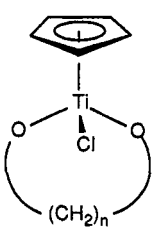
Atom	Charges	
	Mulliken	Lowdin
Ti	+ 1.322	+ 0.675
O	- 0.44	- 0.302
Cl	- 0.44	- 0.452
C(Cp)	- 0.16	- 0.05
$C(CH_3)$	- 0.06	+ 0.03
H(Cp)	+ 0.10	+ 0.07
$H(CH_3)$	+ 0.06	+ 0.03

Minimal Energy Conformations

Conf.	Torsion angle φ		Torsion angle ψ		ΔE
	"si"	*"re"*	*"si"*	*"re"*	(kJ/Mol)
X-ray	79.4	- 179.2	- 7.5	- 2.1	
relaxed	76.3	- 175.3	- 14.5	- 6.9	0.0
# 11	76.9	-174.7	**29.9**	- 6.6	0.0
# 3	**- 170.4**	**72.2**	- 36.3	5.0	- 14.8
# 1	**- 169.9**	-178.4	- 28.0	3.5	- 14.6

The cyclic complex **8** is much more stable towards hydrolysis than **4**, and stirring over night with aqueous NH_4F-solution is needed to liberate the bidentate ligand. Strain energy computations were therefore done for such titanacycles using MACROMODEL (version 2.5) and the charges of the *ab initio* calculation. The results presented in *Figure 3* show, that the 7-membered ring of **8** is in fact optimal. The 6- or 8-membered rings are more strained, and a five-membered dioxa-titanacycle should not be a stable molecule, according to these calculations. An 8-membered representative has recently been described (ref. 28), and 5-membered rings are accessible for octahedrally coordinated Ti-complexes (*e.g.* ref. 62).

Figure 3



	Strain Energy (kJ/Mol)	Ti - O - C angle	O - Ti - O angle
n = 2 5-ring	+ 27.2	126°	79°
n = 3 6-ring	- 22.5	137°	89°
n = 4 7-ring	**- 30.6**	**147°**	**96°**
n = 5 8-ring	- 20.4	148°	99°
n = 6 9-ring	- 10.6	150°	98°
X-ray of **4**		146, 153°	104°
X-ray of **8**		145, 155°	98°

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