Stereoselective transformations mediated by chiral monocyclo-pentadienyl titanium, zirconium, and hafnium complexes

Rudolf O. Duthaler[a]*, Andreas Hafner[b]*, Paul L.Alsters[a], Petra Rothe-Streit[a], and Grety Rihs[c]

[a] Central Research Laboratories, *Ciba-Geigy AG*, Postfach, CH-4002 Basel (Switzerland)
[b] Material Research, *Ciba-Geigy AG*, 1701 Marly (Switzerland)
[c] X-Ray analyses: Physics Department, *Ciba-Geigy AG*, Postfach, CH-4002 Basel (Switzerland)

Abstract: - The chiral cyclopentadienyldialkoxytitanium chlorides 3 and 4 with ligands derived from (*D*)-glucose and tartaric acid afford highly stereoselective reagents for the addition of nucleophiles to aldehydes. The methyltitanium derivatives of 4 are unreactive, but interesting reagents result from mixtures of the chloride 4 and different organometallics before the transmetalation occurs. Most successful for the methyl transfer are, however, the Cp*Zr- and Cp*Hf-analogs of the titanacycle 4. While the cyclic complex 4 is especially suited for the allyltitanation of aldehydes, the diacetoneglucose system 3 is the best choice for aldol reactions. The stereochemical course of these reactions can be rationalized by six-membered cyclic transition states with either chair-conformation in the case of allyltitanations or boat-conformation for the aldolizations. Interactions of the alkoxy ligand(s) with the cyclopentadienyl group seem to be crucial for good stereoselectivity. The mechanism of the often perfect enantiofacial differentiations is, however, still unclear and might be due to stereoelectronic effects. These reagents have been successfully applied for the synthesis of C(2)-modified pentoses from glyceraldehyde.

INTRODUCTION

After many years of academic endeavor the stereocontrol in organic synthesis has become a major issue for the chemical industry as well (refs. 1 and 2). One of the basic processes for inducing optical activity, the stereoselective addition of nucleophiles to prochiral carbonyl groups (ref. 3), can, in the case of organometallics, be controlled efficiently with chiral ligands. The necessary coordinative robustness of such chiral complexes can be obtained either with metalloids such as boron or tin, or with transition metals. Very attractive for their high abundance and low toxicity are the early transition metals titanium and zirconium, which have therefore been used extensively for chiral and achiral modification of C-nucleophiles (refs. 4 and 5), as catalysts for stereoregular polymerization (ref. 6), as chiral *Lewis*-acids (refs. 7 and 8), and for asymmetric epoxidation (ref. 9). The stability, tendency for aggregation, and the reactivity of Ti-complexes is related to the steric and electronic nature of its ligands. In the case of η_1-bound groups the *Lewis*acidity is electronically governed by the bonding atom and decreases in the sequence: halogen > carbon > nitrogen $\approx$ oxygen. A much greater impact on reactivity and selectivity is, however, exerted by η_5-bound cyclopentadienyls, as the formal electronic configuration of titanium is augmented from d^8 to d^{12} upon introduction of one Cp-ligand, and to d^{16} for titanocenes. While chiral titanium complexes with formal d^8-configuration have been successfully applied as chiral *Lewis*-acids (refs. 7 and 8) and for the addition of alkyl groups and other d¹-nucleophiles to carbonyls (*e.g.* refs. 4,5, 10 - 13), the main application of chiral *bis*-Cp compounds is stereoregular polymerization (ref. 6). The chiral monocyclopentadienyl complexes introduced by us (refs. 14 and 15), on the other hand, turned out to be ideal templates for the stereoselective addition of allyl groups (refs. 16 and 17) and ester enolates (refs. 18 - 21) to aldehydes.

SYNTHESIS OF COMPLEXES AND ADDITION OF ALKYL GROUPS TO ALDEHYDES

Due to the stability of the Ti-O bond chiral alcohols are well suited as chiral Ti-ligands. Such groups are best introduced by ligand exchange, *i.e.* substitution of a leaving group X, which can be halogen, an alkyl, or another alkoxy residue, by R*O. The transformation of the precursor **a** via adduct **b** to product **c** is controlled thermodynamically and the equilibria can be displaced to **c** by removal of XH either by evaporation, silylation, or deprotonation (*Scheme 1*, equation (1)). Another possibility is ligand redistribution as depicted by equation (2) (*Scheme 1*). In this case a cyclic dimer **d** is formed from mononuclear complexes **e** and **f**. Cleavage of **d** in the alternative fashion leads to different monomers **g** and **h**. In the case of strongly *Lewis*-acidic compounds, and especially for zirconium complexes, adducts **b** and aggregates such as **d** can be more stable than the monomers (for a more extensive discussion *cf.* ref. 22).

Scheme 1

Diacetoneglucose (2)

(DAGOH)

(*R,R*)-i

(*R,R*)-j

(*R,R*)-4   R$_1$ = C$_6$H$_5$ R$_2$/R$_3$ = CH$_3$
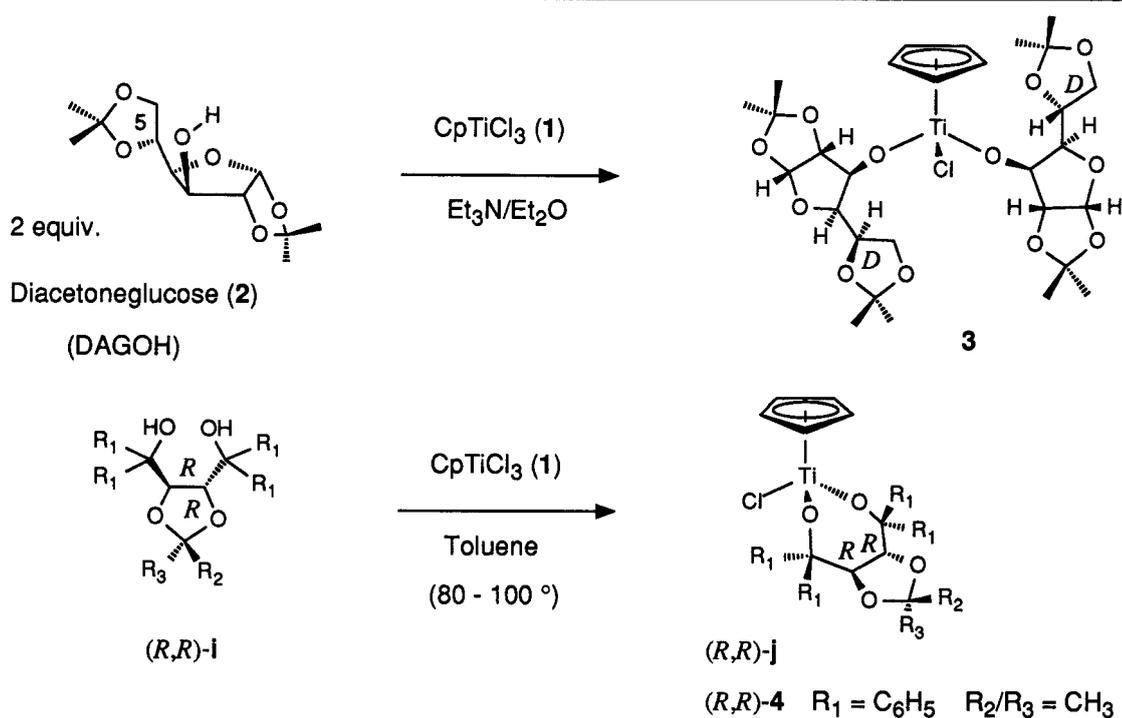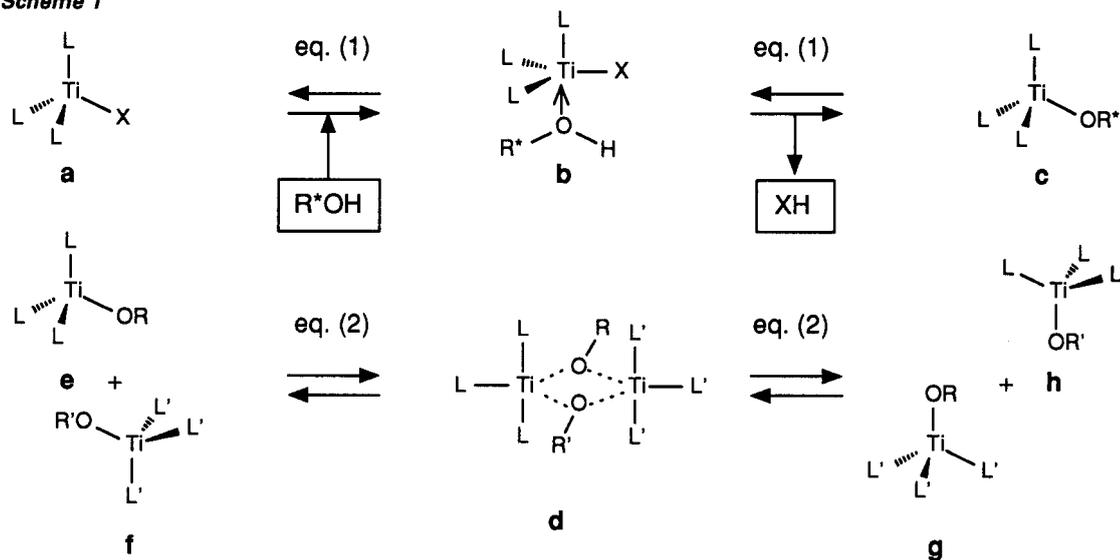
To avoid problems associated with a stereogenic metal center, we prepared chiral monocyclopentadienyl complexes from CpTiCl₃ (1) by substitution of two chlorides with either two identical chiral alkoxides or with a C_2-symmetrical chelating dialkoxide. The remaining chloride can then be replaced by the nucleophilic ligand which is to be added to the carbonyl. Astonishingly only few alcohols and diols are suited for the preparation of stable cyclopentadienyldialkoxytitanium chlorides. So far the best results have been obtained with 1,2:5,6-di-*O*-isopropylidene-α-(*D*)-glucofuranose (diacetoneglucose 2) and with the 1,2-threitol acetals **i**, obtained conveniently in both enantiomeric form from (*R*,*R*)- or (*S*,*S*)-tartrate (ref. 23). The *bis*-diacetoneglucose complex 3 and several of the seven-membered titanacycles **j** (*e.g.* 4) were analyzed by ¹H-, ¹³C-, and ⁴⁹Ti-NMR, as well as by X-ray structure determination (refs. 14, 17, and 24). Seemingly minor modifications of these ligands like inversion of C(5) of diacetoneglucose, the diol **i** with R_1 = H, or other 1,4-diols (*e.g.* β-binaphthol) afford unstable compounds or complex mixtures of oligomeric structures not suited for synthetic transformations.

Scheme 2
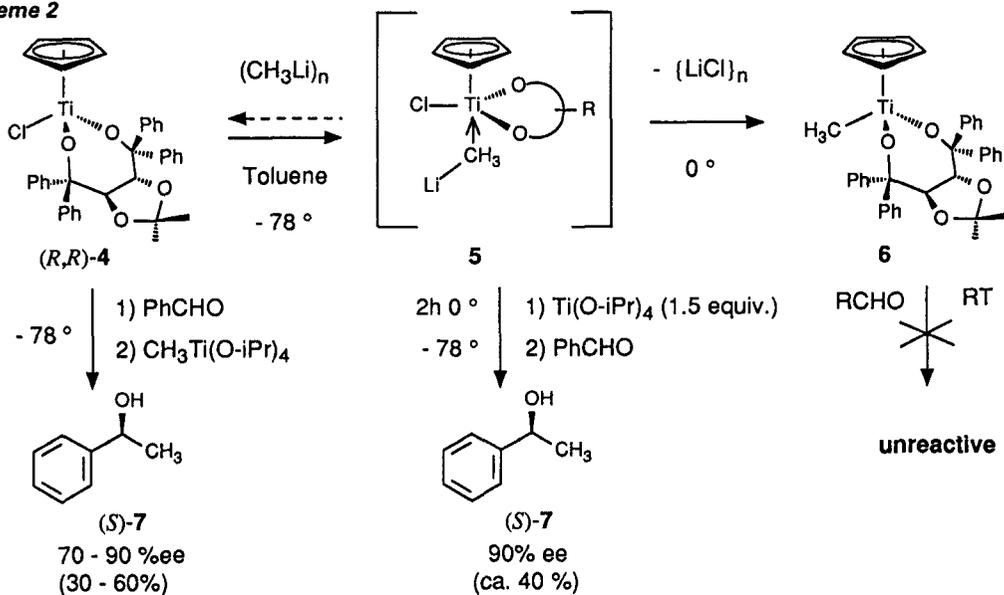
Addition of ethereal CH₃Li to a toluene solution of chloride (*R*,*R*)-4 at - 78 °C gives a clear solution most probably of the adduct **5** or a similar aggregate. Upon warming to 0 °C LiCl is precipitated and the methyl-Ti compound **6** formed can be isolated as an amorphous solid by filtration and evaporation of solvent (*Scheme 2*). According to ¹H- and ¹³C-NMR **6** is either monomeric or a symmetrical oligomer (δ (CH₃Ti): 0,83 ppm/¹H; 43.0 ppm/¹³C). In accordance with the astonishing stability of **6** is its inertness towards aldehydes, and not a trace of product can be observed with benzaldehyde even at room temperature and in the presence of Ti(O-*i*Pr)₄. More promising is the behaviour of the presumed intermediate **5**, which affords racemic 1-phenylethanol (**7**) upon reaction with benzaldehyde at - 78 °C. Treatment of **5** with 1.5 equiv. of Ti(O-*i*Pr)₄ for 2 h at 0 °C not only impedes the formation of **6**, but has a pronounced effect on the stereoselectivity, as (*S*)-7 is now obtained with high enantiomeric purity (90 - 97% ee). Similar induction can also be achieved with chloride (*R*,*R*)-4 and distilled CH₃Ti(O-*i*Pr)₃. In this case it seems to be important that the aldehyde is added to (*R*,*R*)-4 prior to the CH₃Ti(O-*i*Pr)₃ (*Scheme 2*). The yields of these transformations are, however, moderate at best, and not all experimental parameters necessary for good induction are yet identified. Further studies aiming at a better understanding and at possible optimizations of these processes are in progress.

Scheme 3
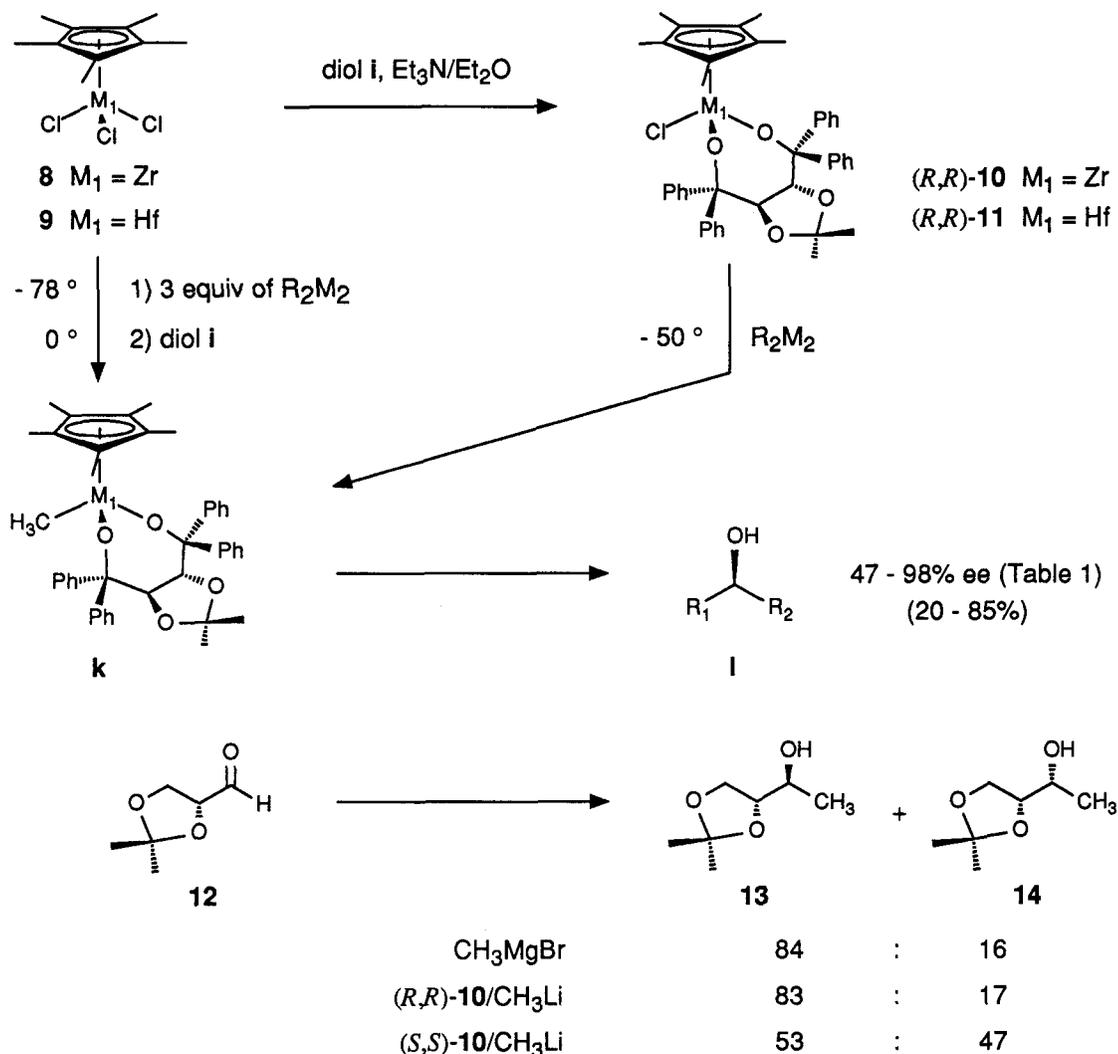
The inertness of the methyltitanium compound **6** is in sharp contrast to related reagents lacking the Cp-ligand (refs. 4, 22, and 25). Due to steric and electronic factors such complexes are not only stronger *Lewis*-acids, better suited for the activation of aldehyde carbonyls, but also show a higher tendency for aggregation. As the transfer of nucleophiles reacting at C(1) (d^1-nucleophiles) to carbonyls is most probably not a bimolecular process (*cf.* refs. 3 and 26), aggregation could be a necessity for reaction. In addition to the ligands such aggregation is also a function of the ionic radius of the metal center. Therefore the analogous Zr- and Hf-complexes should have a higher tendency for aggregation, and may possibly be more reactive than the Ti-compound **6**. As CpZrCl$_3$ cannot be obtained monomeric without an additional coordinating ligand, pentamethyl-cyclopentadienylzirconium trichloride **8** and the hafnium analog **9** were transformed to the metallacycles (*R,R*)-**10** and (*R,R*)-**11**, respectively, characterized by ^{1}H- and ^{13}C-NMR (*Scheme 3*). Transmetalation of **10** and **11** with an alkyl-Li or *Grignard* compound supposedly gives reagents **k**, which then react as expected with aldehydes, affording secondary alcohols **l** in low to good

yield. As shown in *Table 1*, benzaldehyde can be methylated with very high enantioselectivity with either **10** or the hafnium analog **11**. In contrary to the titanium reagents without Cp-ligand (*cf.* refs. 4, 22, and 25) the results do not depend on CH_3M_2, and *Grignard-* or Li-compounds give identical results. Furthermore, an alternative mode of preparation - exchange of all three chlorides of **8** by CH_3, followed by addition of diol **i** - gives almost the same result (90% ee for the reaction with benzaldehyde). However, considerably lower induction is obtained with other alkyl groups than methyl and with other substrates than benzaldehyde, a common feature of many other enantioselective alkylating agents as well (*Table 1*). In the case of the ethyl and butyl complexes better optical yields, achieved by increasing time and/or temperature of the transmetalation, are accompanied by lower chemical yields. In analogy to other systems (*cf.* refs. 12, 25 and 26) these reagents give poor results with more complex aldehydes, especially when chelating heteroatoms are involved. As shown in *Scheme 3*, addition of **10**/CH_3Li to glyceraldehyde acetonide **12** does not surpass achiral reagents in the matched case (*cf.* ref. 27), and for the mismatched pair the ratio of the two diastereomeric products **13** and **14** is close to 1 : 1.

Table 1: Alkylation of aldehydes using the Zr-Complex **10** or the Hf-analog **11** (*Scheme 3*).
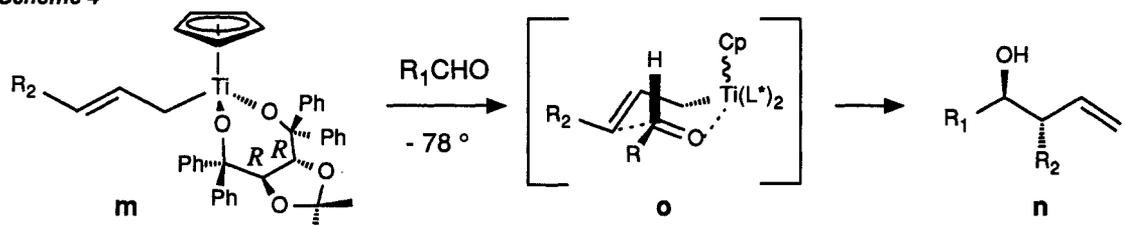
Complex		R_2M_2	Aldehyde	Enantiomeric excess of **l**
(*R,R*)-**10**	M_1 = Zr	CH_3MgBr	Benzaldehyde	98% ee
		CH_3Li	Benzaldehyde	97% ee
		CH_3Li	Decanal	80% ee
		EtMgBr	Benzaldehyde	52 - 81% ee[a]
		n-BuLi	Benzaldehyde	68 - 83% ee[a]
(*R,R*)-**11**	M_1 = Hf	CH_3MgBr	Benzaldehyde	97% ee
		EtMgBr	Benzaldehyde	47% ee
		n-BuLi	Benzaldehyde	65% ee

[a] Variations are related to the transmetalation conditions (*cf.* text).
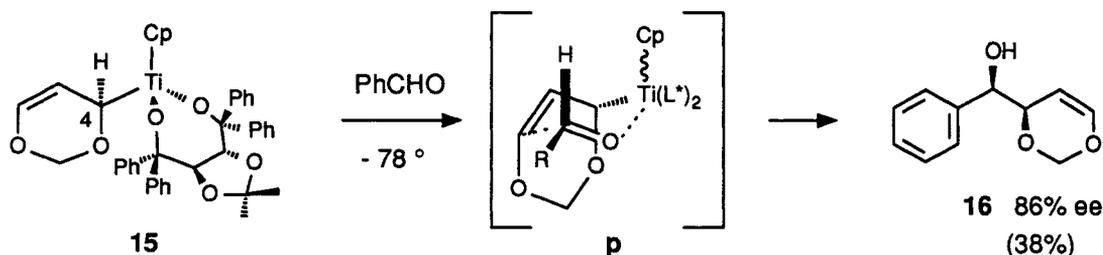
ALLYLTITANATION AND ALDOL REACTIONS

Transmetalation of chloride (*R,R*)-**4** with allylmagnesium chloride, terminally monosubstituted allyl-*Grignard* compounds, or α-lithiated olefins affords the allyltitanium compounds **m** (*Scheme 4*). Very fast 1,3-titanium shift and bond rotation, evidenced by the degenerate ^{1}H- and ^{13}C-NMR signals in case of the unsubstituted allyl complex **m** (R_2 = H), is responsible for the immediate equilibration to the thermodynamically favored *trans*-isomers with titanium bound to the unsubstituted allyl terminal, independent of the isomeric situation of the organometallic precursor. The almost exclusive formation of *anti*-adducts **n** is best rationalized by a cyclic six-membered transition state **o** with chair conformation. Very high *Si*-face selectivity (≥ 95% ee) is induced by the chelating ligand derived from (*R,R*)-tartrate (refs, 15 and 17). *Re*-face preference, on the other hand, is exhibited by the analogous reagents derived from the diacetoneglucose complex **3** (ref. 16). In this case the enantioselectivities are somewhat lower, and for difficult substrates like 2-phenylbutyraldehyde (*cf.* ref. 17) the *Re*-selective reagent derived from (*S,S*)-tartrate might be preferable to the diacetoneglucose system.
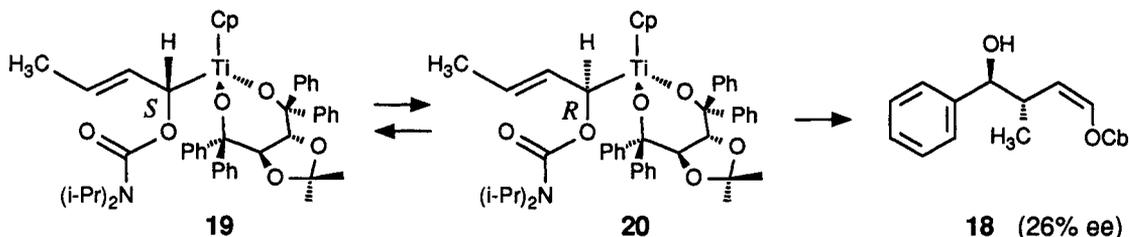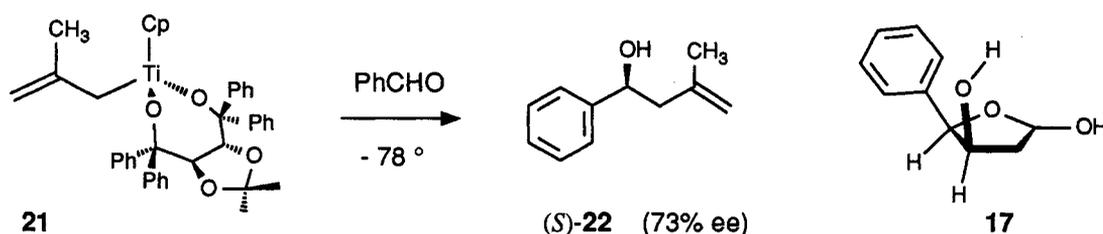
Scheme 4

R$_2$: H, CH$_3$, CH=CH$_2$, C$_6$H$_5$, SiMe$_3$, OC$_6$H$_4$OCH$_3$

95 - 98% isomeric purity

16 86% ee
(38%)

hydrolysis

(S)-22 (73% ee)

17

(i-Pr)$_2$N
19

(i-Pr)$_2$N
20

18 (26% ee)

The mechanistic picture is further corroborated by the titanated 2,4-dihydro-1,3-dioxin **15**, which affords exclusively the *syn*-isomer **16** upon reaction with benzaldehyde (*Scheme 4*). The low yield (38%) is due to the transmetalation step, and the potential for optimization can be considered as good. The relative configuration of **16**, determined by NOE-measurements of the derivative **17**, can again be rationalyzed by a chair transition state **p**. The absolute configuration of **16** is directly related to the C(4)-configuration of reagent **15**, and has not been verified yet. The stereochemistry of **15** and the enantiofacial preference of the addition are both steered by the chiral ligand, and the slightly inferior enantioselectivity (86% ee) , when compared to the results with monosubstituted allylreagents **m**, might reflect an antagonism of the two influences. This is more pronounced, when the *Hoppe*-homoenolate (ref. 28) is transmetalated with (*R,R*)-**4**. The exclusive formation of the *anti*-isomer with *cis*-double bond **18** of low optical purity (26% ee) could be due to an equilibrium of stereoisomeric allyltitanium species **19** and **20** (*Scheme 4*). In contrary to the allylboron reagents (*cf.* refs. 29 - 32) substitution of the central carbon of the allyl group is re-

ducing the stereoselectivity of these allyltitanium reagents. Addition of the tartrate derived methallyl complex **21** to benzaldehyde affords (*S*)-**22** of 73% ee; in case of the diacetoneglucose analog (*R*)-**22** is obtained with 38% ee only.

Scheme 5
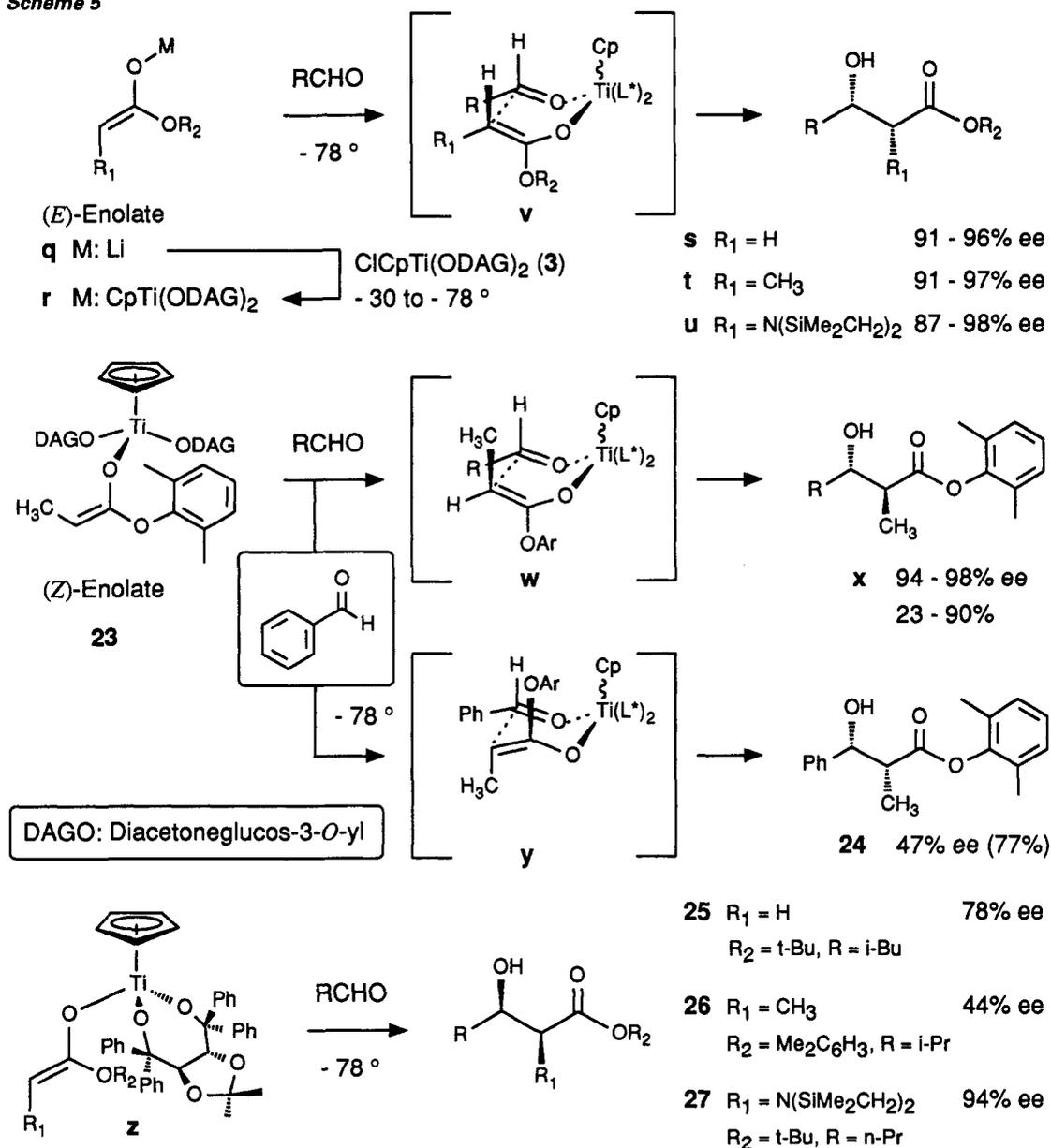
The aldol reaction is one of the most predictable C-C bond forming processes, and Ti-enolates are now used frequently to control the diastereoselectivity of this reaction (*e.g.* refs. 33 - 36). A cyclic six-membered transition state is invoked for most cases, and therefore the aldol reaction is mechanistically related to the addition of allylic nucleophiles to aldehydes. Lithium enolates can be transmetalated at low temperature (- 30 to -78 °C) with cyclopentadienyldialkoxytitanium chlorides. Thus, ester enolates **q** afford the chiral Ti-enolates **r**, when treated with the diacetoneglucose complex **3** (*Scheme 5*). As one of the main driving forces of the allyltitanation, the transfer of titanium from carbon to oxygen, is missing, Ti-enolates are less reactive than allyl-Ti compounds. Therefore ketone-enolates and enamides prepared from

chloride **3** are unreactive, and only the more nucleophilic ester enolates **r** react with aldehydes at - 78 °C. The acetate, propionate, and glycine aldols **s** (refs. 18 and 20), **t** (ref. 21), and **u** (ref. 19) are obtained with excellent enantioselectivity, the *Re*-side of the aldehyde carbonyl being attacked preferentially (*Scheme 5*). As opposed to the allyltitanation (*cf. Scheme 4*) a boat transition state **v** has to be assumed to explain the high *syn*-selectivity of pure (*E*)-enolates **r**. More astonishing is the fact that (*Z*)-enolates, such as the propionate-enolate **23**, obtained by equilibration of the corresponding (*E*)-enolate **r** (ref. 21), also react via a boat transition state **w**, affording *anti*-aldols **x** of high optical purity. In the case of benzalde-hyde and other substrates with a branched sp^2-α-carbon a chair transition state **y**, giving the *syn*-aldol **24** with low enantioselectivity (47% ee), accounts for 77% of the product mixture in addition to only 23% of *anti*-aldol **x** of 94% ee (*Scheme 5*). The enolate **23** was the first example of an *anti*-selective (*Z*)-enolate (ref. 21); since then two additional examples have been identified (refs. 37 and 38).

The titanium enolates **r** and **23** are among the most stereoselective reagents known. However, as (*L*)-glu-cose is not readily available, the preparation of the enantiomers of **s**, **t**, **u**, and **x** is highly inpracticable by this method. As exemplified by the aldols **25** and **26**, the cyclic complex (*R,R*)-**4** is not suited as a templa-te for enantioselective acetate and propionate aldol reactions (*cf.* ref. 22). So far the only exception is the (*L*)-configurated *threo*-β-hydroxy-α-aminoacid **27**, obtained with 94% ee from the Ti-enolate **z** with the (*R,R*)-tartrate derived ligand.
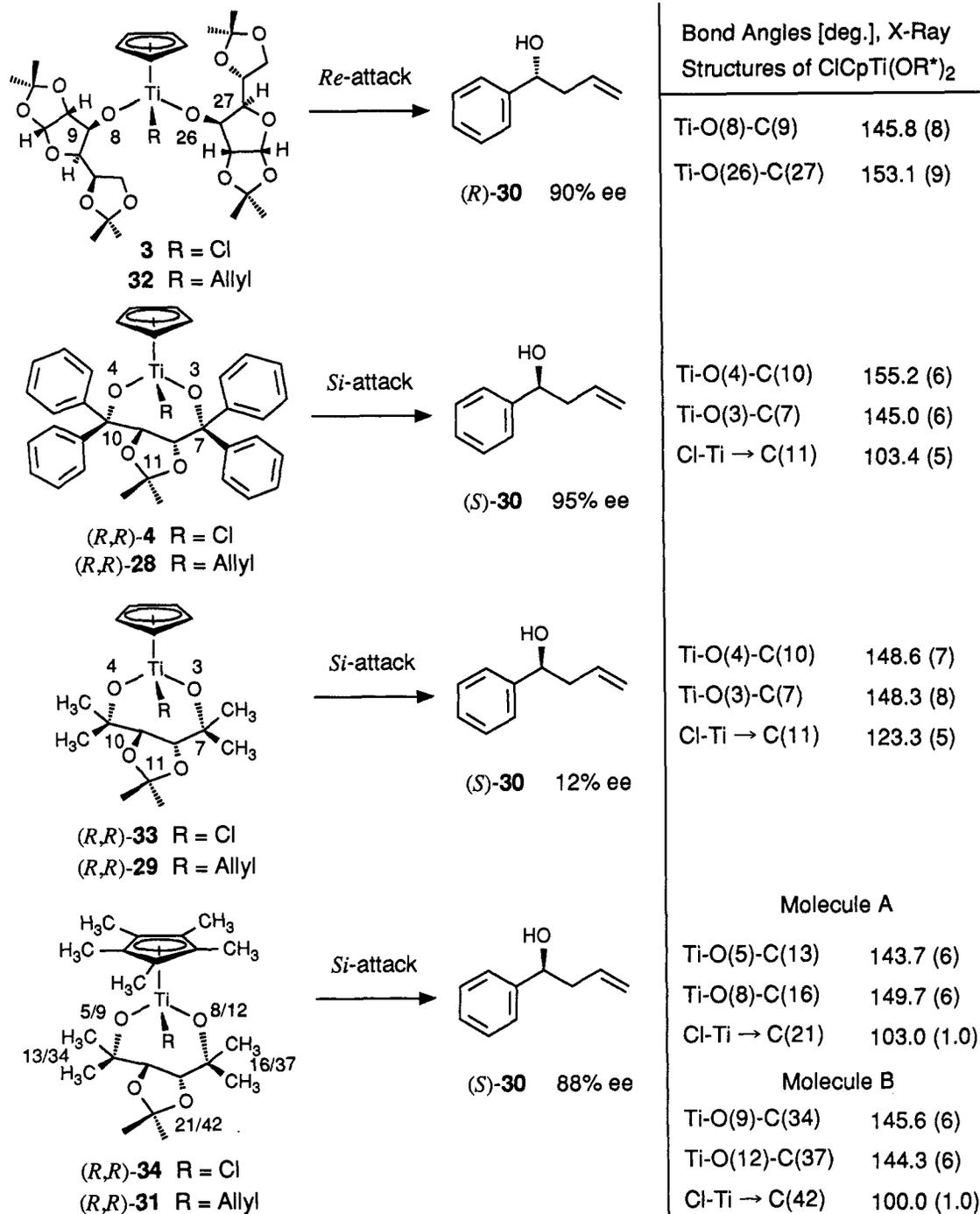
MECHANISTIC CONSIDERATIONS

With the diacetoneglucose complex **3** and the seven-membered titanacycle **4** excellent templates for enantioselective allyltitanations of aldehydes and for enantioselective aldol reactions have been discove-red. In the course of the search for *Si*-selective complexes and better *Si*-selective Ti-enolates several other chiral monohydric ligands and 1,4-diols, as well as substituted cyclopentadienyl groups were tested (*cf.* refs. 15, 17, and 22). While diacetoneglucose is still the only successful example among monodentate ligands, variation of the cyclic complex **4** led to interesting observations. In contrary to the substituents of the acetal carbon, which have only a marginal influence on the stereoselectivity, the size of the geminal substituents of the α-carbons is essential for good induction. Replacement of the phenyl groups of the al-lyltitanium reagent (*R,R*)-**28** by methyls (→ (*R,R*)-**29**) reduces the optical purity of the product (*S*)-**30** from 95 to 12% ee. The enantioselectivity can, however, be restored to a large extent (88% ee), if the cyclopentadienyl ring is replaced by the bulkier pentamethylcyclopentadienyl ligand (→ (*R,R*)-**31**, *Sche-me 6, cf.* ref. 17). This is a clear indication that the scalar magnitude of the enantiofacial discrimination is significantly influenced by interactions between the η_5-bound cyclopentadienyl group and the alkoxy li-gand(s).

The correlation of these ligand-ligand interactions with the sense of induction, *Re*-preference of **32** *vs. Si*-preference of (*R,R*)-**28**, is, however, difficult and no satifying answer can be given yet. More information is provided by the crystal structures of the chlorides **3** (ref. 14), (*R,R*)-**4** (ref. 17), (*R,R*)-**33** (ref. 17), and (*R,R*)-**34** (new). While the two diacetoneglucose ligands of **3** form a highly asymmetric environment ("chiral pocket") around the Ti-Cl bond, the Ti-Cl bonds of the cyclic complexes (*R,R*)-**4**, (*R,R*)-**33**, and (*R,R*)-**34** are not only sterically uncongested, but the four α-C substituents are arranged symmetrically with respect of the Cl-Ti-$Cp_{centroid}$ plane (*cf.* refs. 17 and 22). A C_2-symmetrical or skew conformation, which is often considered essential for the transmission of chirality by C_2-symmetrical complexes (*cf.* refs. 7, 12, and 23), is clearly not exhibited by these titanacycles (*cf.* refs. 15, 17, 22, and 24). As opposed to direct interactions between the chiral ligands and the reacting groups, ligand-ligand interactions could

in principle also induce an electronic distortion of the Ti-coordination geometry, which then would account for the enantioselectivity. The allyl-molybdenum reagent recently described by *Faller* and coworkers is a clearcut example of such stereoelectronic enantioselectivity (ref. 39). In this case the high induction (98% ee) can only be explained by electronic dissymmetry, which is clearly seen in the X-ray structure of this reagent with a η_3-bound crotyl ligand.

Scheme 6

Bond Angles [deg.], X-Ray Structures of ClCpTi(OR*)$_2$	
Ti-O(8)-C(9)	145.8 (8)
Ti-O(26)-C(27)	153.1 (9)
Ti-O(4)-C(10)	155.2 (6)
Ti-O(3)-C(7)	145.0 (6)
Cl-Ti → C(11)	103.4 (5)
Ti-O(4)-C(10)	148.6 (7)
Ti-O(3)-C(7)	148.3 (8)
Cl-Ti → C(11)	123.3 (5)
Molecule A	
Ti-O(5)-C(13)	143.7 (6)
Ti-O(8)-C(16)	149.7 (6)
Cl-Ti → C(21)	103.0 (1.0)
Molecule B	
Ti-O(9)-C(34)	145.6 (6)
Ti-O(12)-C(37)	144.3 (6)
Cl-Ti → C(42)	100.0 (1.0)

Re-attack → (R)-**30** 90% ee

Si-attack → (S)-**30** 95% ee

Si-attack → (S)-**30** 12% ee

Si-attack → (S)-**30** 88% ee

3 R = Cl
32 R = Allyl

(R,R)-**4** R = Cl
(R,R)-**28** R = Allyl

(R,R)-**33** R = Cl
(R,R)-**29** R = Allyl

(R,R)-**34** R = Cl
(R,R)-**31** R = Allyl

As the linewidt of the ^{49}Ti-NMR signals is directly related to the electronic symmetry at titanium, these values should be a qualitative measure of the electronic distortion of closely related structures. ^{49}Ti-NMR measurements of a variety of such complexes confirmed this hypothesis, as a considerable variation in linewidths was found (ref. 17). At least the comparison of (R,R)-4, the precursor of highly selective reagents ($v^{1/2}$ = 3460 Hz), with the nonselective complex (R,R)-33 ($v^{1/2}$ = 1080 Hz) might be significant with respect of such a correlation of enantioselectivity with electronic distortion.

Until very recently, before the crystal structure of (R,R)-34 was available, we also considered the Ti-O-C(α) bond angles as a significant measure for electronic distortion in relation to enantioselectivity (cf. refs. 15, 17, and 22). As opposed to the unselective structure (R,R)-33, the chlorides 3 and (R,R)-4 exhibit significant differences between the two Ti-O-C(α) angles, which have a enantiotopic relation with respect to the Cl-Ti-Cp$_{centroid}$ plane. According to the orientation of Scheme 6, the more obtuse angle of the Re-selective complex 3 is on the right side, while the larger value is measured on the left side of the Si-selective structure (R,R)-4. The data of the new crystal structure of (R,R)-34, however, clearly demonstrate, that the magnitude of these angle-differences is in the range of crystal-packing effects. Good enantioselectivity is obtained with reagents derived from (R,R)-34 and yet one of the two molecules (B) of the unit cell is not distorted with respect of the Ti-O-C(α) bond angles, and the other (molecule B) does not correlate with the sense of distortion of 3 and (R,R)-4, as the more obtuse angle of this Si-selective complex is on the right side (Scheme 6).
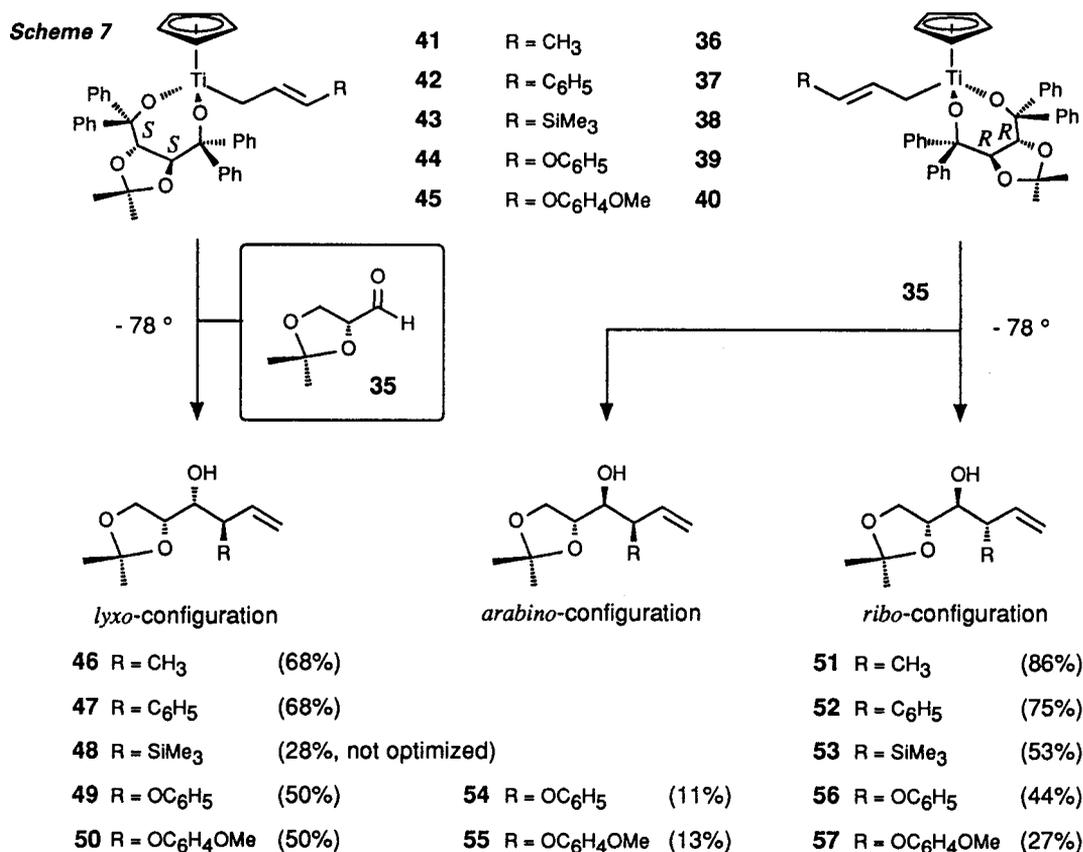

(R,R)-33   (R,R)-34 (molecule A)
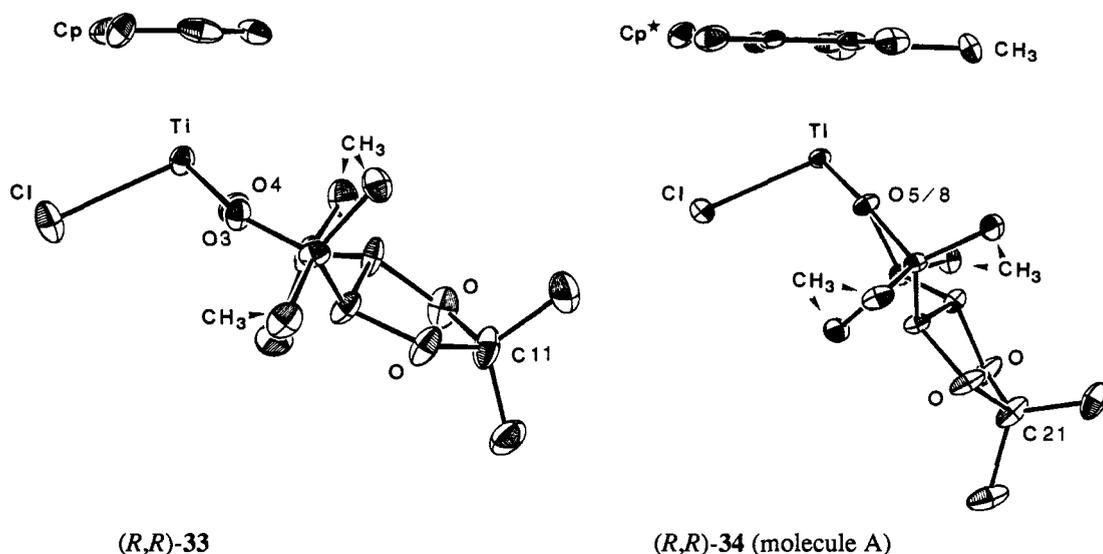
Figure 1: ORTEP-drawings of the crystal structures of (R,R)-33 and (R,R)-34 (molecule A), with vibrational ellipsoids at the 20% probability level.

The effect of the interaction between the Cp-group and the alkoxy ligands is clearly reflected by the orientation of the titanacycle in relation to the Ti-coordination geometry. A good measure for this effect is the angle formed by the chloride, titanium, and the acetal carbon (C(2) of the dioxolane) of the ligand, which is listed in Scheme 6. In the complexes which afford enantioselective reagents, (R,R)-4 and (R,R)-34, the chelate ring is forced away from the cyclopentadienyl ligand. The value of the Cl-Ti→C$_{acetal}$ angle, which is 123.3° in the case of the unselective structure (R,R)-33, is reduced to 100 - 103.3°. This effect is also evident from the ORTEP-representation of (R,R)-33 and (R,R)-34 (Figure 1).
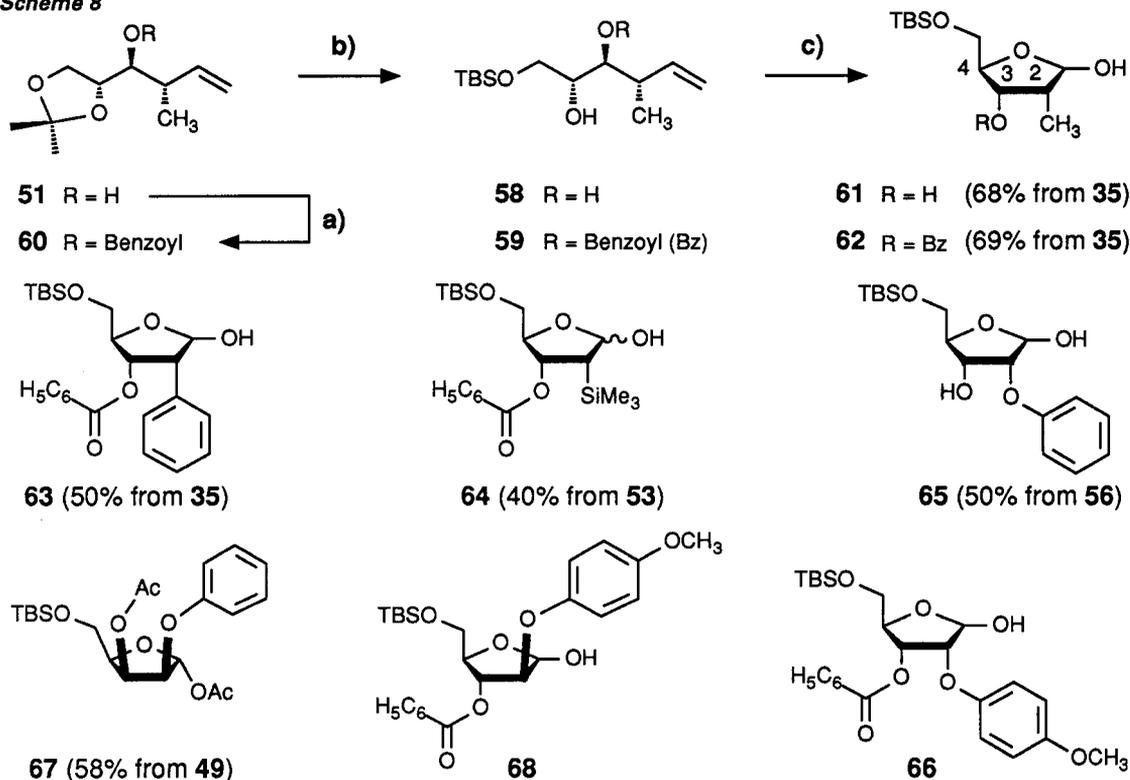
STEREOSELECTIVE SYNTHESIS OF C(2)-MODIFIED PENTOSES

A lot of research effort is presently invested into the possibility of controlling gene-expression with "anti-sense" oligonucleotides (ref. 40). 2'-*O*-Alkylation of ribosides is a most useful principle for backbone modification, as both, the duplex energy and the stability against enzymatic degradation, of such oligo-nucleotides is enhanced (ref. 41). While such 2'-*O*-methyl or 2'-*O*-allyl derivatives are best prepared by *O*-alkylation of ribonucleosides or other ribose derivatives, different C(2')-modifications, which might be interesting as well, can only be prepared by *de novo* synthesis. (*D*)-Pentoses are best prepared by partial synthesis from (*D*)-glyceraldehyde **35** (refs. 42 - 46), a chiral building block, which is conveniently pre-pared from (*D*)-mannitol on a large scale as well (ref. 47). However, the stereoselectivity of additions to **35** is difficult to control, as *Si*-addition is the favored mode of addition for most nucleophiles (refs. 27 and 43). Since we had already found, that **35** can be allylated with perfect diastereoselectivity using ei-ther (*R,R*)-**28** or (*S,S*)-**28** (ref. 17), we reasoned, that substituted allylreagents **m** (*cf. Scheme 4*), obtained by transmetallation with chloride (*R,R*)-**4** or (*S,S*)-**4**, should also add to **35** with high stereocontrol, affor-ding *anti*-products with *ribo*-configuration from (*R,R*)-**4**, or the corresponding *lyxo*-isomers in the case of (*S,S*)-**4**.

Scheme 7

41	R = CH₃	**36**	
42	R = C₆H₅	**37**	
43	R = SiMe₃	**38**	
44	R = OC₆H₅	**39**	
45	R = OC₆H₄OMe	**40**	

lyxo-configuration

46	R = CH₃	(68%)
47	R = C₆H₅	(68%)
48	R = SiMe₃	(28%, not optimized)
49	R = OC₆H₅	(50%)
50	R = OC₆H₄OMe	(50%)

arabino-configuration

54	R = OC₆H₅	(11%)
55	R = OC₆H₄OMe	(13%)

ribo-configuration

51	R = CH₃	(86%)
52	R = C₆H₅	(75%)
53	R = SiMe₃	(53%)
56	R = OC₆H₅	(44%)
57	R = OC₆H₄OMe	(27%)

For this purpose the (*R,R*)-configurated allyltitanium reagents **36** - **40** and the corresponding (*S,S*)-enan-tiomers **41** - **45** have been prepared and used for transformations of (*D*)-glyceraldehyde acetonide (**35**) (*Scheme 7*). As expected the diastereoface selectivity of the additions to the aldehyde carbonyl was ex-cellent and exclusive *Si*-face addition was observed for **36** - **40**, *Re*-face addition for **41** - **45**. While all reagents with the (*S,S*)-configurated ligand (**41** - **45**) and the (*R,R*)-configurated complexes **36** - **38** yiel-ded essentially one product with relative *anti*-configuration of the newly formed sterocenters (compounds

46 - 53), the *syn*-diasteromers **54** and **55** were formed as byproducts of the major *anti*-isomers **56** and **57**, obtained from the reactions of the phenoxy substituted allyltitanium compounds **39** and **40** with (*R,R*)-configuration (*Scheme 7*). After *O*-benzoylation these mixtures could be separated either by chromatography (**55/57**) or by crystallization (**54/56**). The yields of the methyl or phenyl substituted adducts **46, 47, 51,** and **52** is good and distillation of crude material at high vacuum suffices for purification. In the other cases the yields are lower, but improvements should be possible either by using more than 1.3 equiv. of the Ti-reagents, or by optimization of the lithiation and/or transmetalation step.

Scheme 8

51 R = H
60 R = Benzoyl

58 R = H
59 R = Benzoyl (Bz)

61 R = H   (68% from **35**)
62 R = Bz (69% from **35**)

63 (50% from **35**)

64 (40% from **53**)

65 (50% from **56**)

67 (58% from **49**)

68

66

a) Benzoyl chloride/pyridine. b) 1. CH₃OH/CF₃OH (or Amberlyst-15); 2. t-Butyldimethylsilyl-triflate/Et₃N, CH₂Cl₂. c) 1. O₃/CH₃OH, - 78 °C; 2. Me₂S, - 78 °C to room temp.

As exemplified for the crotyl adduct **51**, these glyceraldehyde derivatives could be transformed straight-forwardly to 2-deoxy-2-substituted furanoses with (*D*)-*ribo*-configuration. Especially rewarding is the possibility of selective *O*(3)- and *O*(5)-protection (*Scheme 8*). The most critical step of this sequence is the selective cleavage of the acetonide, which was best performed with a strong protic acid (CF₃SO₃H or *Amberlyst-15*) in CH₃OH. Selective silylation of the primary alcohol gave **58** from **51** and **59** from the benzoylated derivative **60**. The target ribofuranoses **61** and **62** were isolated in excellent overall yield after ozonolysis and reductive workup. The mixtures of α- and β-anomers were not separated and the configuration of C(2) and C(3) in relation to C(4) was determined by NOE-measurements. The 2-deoxy-2-phenyl-, 2-trimethylsilyl-, and 2-phenoxy-, and 2-(4'-methoxy-phenoxy)-ribose, as well as the 2-deoxy-2-phenoxy-lyxose and 2-deoxy-2-(4'-methoxyphenoxy)-arabinose derivatives **63** - **68** were obtained analogously (*Scheme 8*). Due to facile benzoyl and silyl migration, the acyclic intermediates are rather sensitive and chromatographic purification is not recommended before cyclization to the furanoses. For this

reason the 3-*O*-benzoylated derivative of **65** and **67** could not be prepared. The selective ozonolysis of a double bond in the presence of an electronrich p-methoxyphenyl ether was successful for the preparation of **66** and **68** from **57** and **55** but failed in the case of the lyxose derivative **50** (*Scheme 7*). Therefore compound **49** was converted to 2-*O*-phenyl-lyxose **67**, which was isolated as pure α-anomer after acetylation. *Peterson*-olefinations complicated all transformations of the trimethylsilyl derivative **53**. Only one anomer of **64** turned out to be stable. A major byproduct of the oxidative degradation, 2,3-dideoxy-2,3-dehydro-ribonolactone, most probably arises from the other anomer by eliminations. Most of these conversions have not been optimized, and were carried out only once, to determine the configuration of the products obtained by the allyltitanation. Due to the high selectivities and the potential for further modifications, this scheme for the preparation of unusual pentoses from glyceraldehyde compares favorably with other closely related methods (*cf.* refs. 42 - 46, 48, and 49).

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