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Carbohydrate phosphinites as chiral ligands for asymmetric synthesis catalyzed by complexes

VI *. Rhodium(I)-[2,3-*O*-bis(diphenylphosphino)-β-D-glucopyranoside] chelates with free hydroxyl groups in the 4,6-positions of the carbohydrate as excellent catalysts in asymmetric hydrogenation

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Abstract

The application of rhodium(I) complexes **4** carrying 2,3-bis(diphenylphosphino)-β-D-glucopyranoside ligands having free hydroxyl groups in the 4,6 positions has been investigated. The complexes **4** as catalysts result in greater optical induction in the hydrogenation of methyl (*Z*)-acetamidocinnamate **1d**, in all seven solvents used, relative to the precursor complexes **3** with the 4,6-positions protected by an acetal ring. The (*S*)-enantioproductivity q_S (ratio of the enantiomers produced, *S*: *R*) doubles when precatalyst **4b** is used. It triples in the case of the analogous phenyl-*C*-glucopyranoside, **4c**. For the acid substrate **1b** the differences are less distinct showing only one exceptional case in dioxane as solvent. The importance of the relatively bulky equatorial pyranoside substituents, such as R^1, OH and CH_2OH, for the high enantioselectivities of the complexes **4** is striking.

Introduction

According to an early hypothesis of Kagan [2] a high degree of stereoselectivity in asymmetric catalysis requires chelates, in which the *strongly bonded* chiral ligand should have a *conformation of maximum rigidity*. Kagan verified this postulate by successfully preparing the ligand diop with the trans-configurational dioxolane ring in the backbone. However, some chiral ligands lacking rigid, condensed ring in the backbone are known, and form the large, high reactive 7- or 8-membered ring

* For part V see ref. 1.

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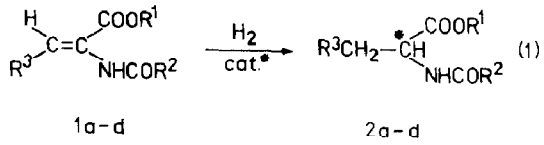
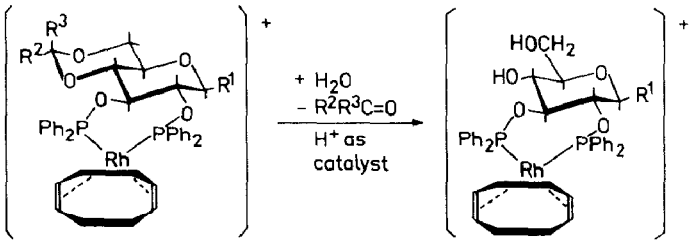
chelates [3,4] giving high enantioselelctivities of about 95% ee of **2b** in the asymmetric hydrogenation of *N*-acyl-dehydroamino acid **1b** according to equation 1 [3,4].



1a–d 2a–d

	R^1	R^2	R^3
a	H	Me	H
b	H	Me	Ph
c	Me	Me	H
d	Me	Me	Ph

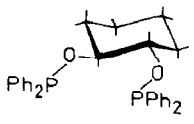
In our attempts to develop chiral chelating ligands using carbohydrates as variable and cheap precursors of the chiral pool we started with pyranosides protected in the 4- and 6-positions by a benzylidene-acetal ring to give 2,3-*O*-bis(diphenylphosphino) ligands [5]. The best example, phenyl 4,6-*O*-(*R*)-benzylidene-2,3-*O*-bis(diphenylphosphino)-β-D-glucopyranoside (Ph-β-glup) forms the cationic chelates **3a**, which in asymmetric hydrogenation provide outstanding enantioselectivities of 96–99% ee (*S*)-*N*-acylamino acid **2a**,**2b**. The high activity of the precatalyst **3a** enabled an industrial application to produce L-dopa [6]. The importance of all-equatorial substituents for highest optical induction has been described [7].



(2)

	R^1	R^2	R^3			R^1
3a	OPh	Ph	H	→	4a=4b	OPh
3b	OPh	Me	Me	↗		
3c	Ph	Me	Me	→	4c	Ph

The rigidity in the Ph-β-glup chelates **3a** originating from the $^4C_1$-pyranoside ring in the backbone should be additionally fixed by the condensed *m*-dioxane ring. The question arises, of whether this type of ligand with an additionally condensed ring really does ensure maximum enantioselectivity compared with similar ligands without that second stiffening ring. Rhodium chelates of ligands **5** and **6** without further substituents on cyclohexane gave optical yields lower than 69% ee [8] and 36% ee (*S*)-**2b** [9,10] respectively. Though the conditions for the early hydrogenation measurements had little in common, the rigid *m*-dioxane ring in Ph-β-glup results in greatly improved enantioselectivity of its rhodium chelates **3a**. However, comparison with the new easily accessible chelates **4** [1] of glucopyranoside-bis(phosphinites) carrying free hydroxy groups in the 4,6 positions presented some surprising revelations in regard to the above question.



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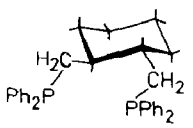

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Results and discussion

A comparison was made of the enantioselectivities of the two complexes **3a** and **4b**, as precatalysts for the hydrogenation of (*Z*)-acetamidocinnamic acid **1b** in dioxane, and the distinct decrease by 15.1% ee [from 91.3 to 76.2% ee (*S*)-**2b**] implicates the *m*-dioxane ring in chelate **3a** as the reason for its greater enantioselectivity. However, this may be exceptional, in that the results in Table 1 lead to an inverse conclusion. In methanol as solvent, the difference in enantioselectivities is only about 2% ee, and the same is true of the analogous couple of phenyl-*C*-glucopyranoside chelates **3c** and **4c** in methanol as well as in dioxane. In general, the half-life lies between 2 and 4 minutes, a state in which diffusion of H_2 becomes rate determining.

For the hydrogenation of the analogous ester **1d** we obtained more uniform results (Table 2). The parallellism of the curves of enantioselectivity obtained for all five investigated complexes **3a–3c** and **4b,4c** is striking. From Fig. 1, in which the solvents used are arranged in order of polarity (E_T-values [11]), the following can be deduced:

(i) All five complexes show their highest optical induction in alcohols as solvents. Satisfactory values are obtained in tetrahydrofuran and in most cases in aromatic hydrocarbons. The minimum enantioselectivity in dioxane is unexpected, as even in dioxane especially high % ee values of up to 95% ee (*S*)-**2b** were found for aminophosphinephosphinite chelates * [12].

(ii) In all solvents investigated the two complexes **4b** and **4c** with unprotected ligands carrying free hydroxyl groups in the 4,6 positions of the glucopyranoside moiety show the highest % ee **. There is no significant effect by R^1 (comparing only OPh and Ph; Δ% ee: 0.9 ± 0.5%).

Table 1

Comparison of the enantioselectivities (% ee) of the complexes **4a–4c** carrying free hydroxyl groups and the complexes **3a–3c** with intact *m*-dioxane ring ligands in the asymmetric hydrogenation of 1 mmole of the acid **1b**. Complex 0.01 mmole, 15 ml solvent, 0.1 MPa H_2, 25 °C

Solvent	Complex				% ee (*S*)-**2b**		Δ% ee
	n	R^1	R^2	R^3	***4n***	***3n***	(***4n*** – ***3n***)
dioxane	**a**	OPh	Ph	H		91.3	−15.1
dioxane	**b**	OPh	Me	Me	76.2	89.4	−13.2
dioxane	**c**	Ph	Me	Me	87.3	89.8	−2.5
methanol	**a**	OPh	Ph	H		96.6	−1.5
methanol	**b**	OPh	Me	Me	95.1	95.4	−0.3
methanol	**c**	Ph	Me	Me	94.6	93.5	1.1

* However, recently we showed that in this case a solvolytic change of the aminophosphine-phosphinite chelates catalyzed by protons of the acid substrates causes the partial destruction of the hydrogenating catalyst by protic solvents, which is not evident in nonprotic ones such as dioxane. This would explain similarity of the results of Pavlov et al. [13] for the chelates of PheNOP without assuming changes in the hydrogenation mechanism.

** This explains a singular effect: Cationic Ph-β-glup chelates immobilized on H^+ cation exchangers lead to higher optical induction (94.3 ± 0.5% ee) in the hydrogenation of **1d** in methanol than the homogeneous soluble Ph-β-glup chelates **3a** [91.5 ± 0.5% ee (*S*)-**2d**] [14]. The reason for this unexpected effect is the rapid solvolysis of the acetal ring of the catalyst by methanol under catalytic action by the protons from the exchanger to give immobilized **4b** with greater enantioselectivity.

Table 2

Comparison of the enantioselectivities (% ee) of corresponding complex pairs (**3** and **4**) in the hydrogenation of the prochiral ester **1d**. Substrate 1 mmole, complex 0.01 mmole, 15 ml solvent, 0.1 MPa H_2, 25 °C. The observed standard deviation is ±0.5% ee (GLC)

Solvent	**3a**		**3b**		**4b**		4b-3b	**3c**		**4c**		4c-3c
	$t/2$ (min)	%ee (*S*)	$t/2$ (min)	%ee (*S*)	$t/2$ (min)	%ee (*S*)	Δ %ee	$t/2$ (min)	%ee (*S*)	$t/2$ (min)	%ee (*S*)	Δ %ee
MeOH	6	91.5	5	91.3	3	94.8	3.5	6	85.9	4	94.1	8.2
EtOH	3	91.5	7	92.4	3	95.8	3.4	2	86.9	3	94.6	7.7
i-PrOH	3	91.6	5	92.8	2	95.6	2.8	2	87.8	2	94.0	6.2
THF	4	86.1	3	86.9	3	94.5	7.6	2	79.9	2	93.5	13.6
dioxane	3	79.0	4	79.1	3	88.0	8.9	3	74.0	2	89.3	15.3
benzene	7	81.0	3	80.8	5	92.1	11.3	3	73.9	6	92.6	18.7
toluene	6	81.0	4	81.8	48	91.6	9.8	3	74.9	33	92.9	18.0

(iii) However, the enantioselectivities of complexes **3a–3c** carrying the 4,6-*O*-alkylidene-protected ligands are dependent on the R^1 group. The complex **3c** with R^1 = Ph (*C*-glucopyranoside) shows the lowest % ee and differs from that of 3b by an almost constant value, Δ % ee: 6.0 ± 1.0%.

(iv) The nature of the 4,6-*O*-alkylidene group originating from benzaldehyde or acetone has no effect on the enantioselectivity [Δ% ee (**3a–3b**): 0.6 ± 0.5%]. This is

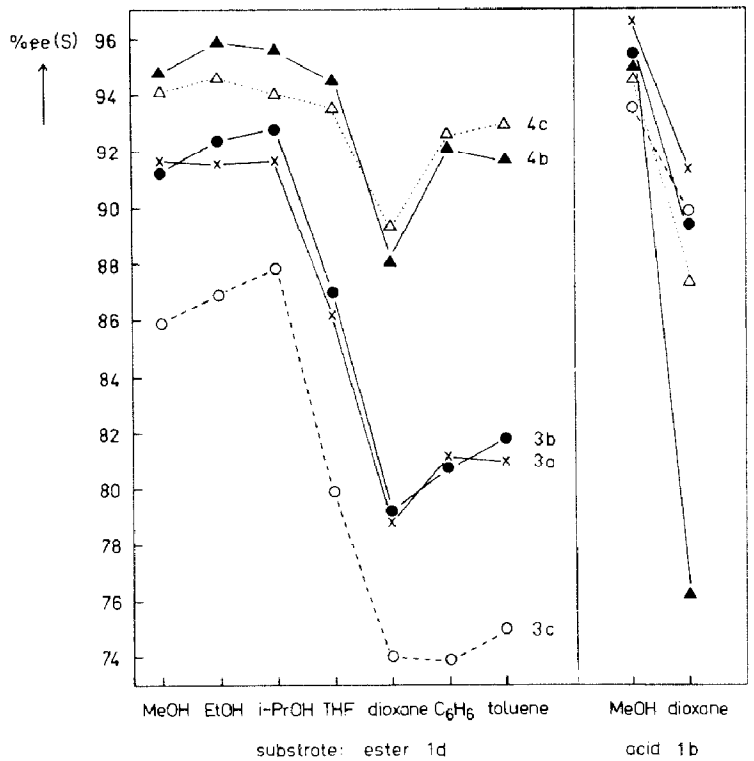
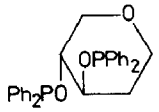


Fig. 1. Dependence of the enantiomeric excess, resulting from asymmetric hydrogenations with the chelates **3a–3c** and **4b**,**4c**, on the solvent applied.

plausible owing to the large distance from the centre of the reaction, but could change with more bulky axial R^3 group greater with resultant strong influence on the $^4C_1$-conformation of the glucopyranoside ring.

(v) With less polar solvents, the Δ% ee-values for the **4**/**3**-couples [Δ% ee (**4b-3b**): 3 to 11%, (**4c-3c**): 6 to 19%] show a distinct increase starting from isopropanol and reaching a maximum in benzene (see Table 2). However, this may be misleading because the value of the enantiomeric excess (% ee) in several regions does not give a good indication as to the true microscopic events. We propose the enantioproductivity ($q_S = 1/q_R = S/R$) to be a convenient measure of enantioselectivity; the quotient Q of two enantioproductivities ($Q_S = q_S\mathbf{4}/q_S\mathbf{3}$) to be a direct measure of an altered ability on the microscopic scale is more suitable for comparing the optical induction of two chelates, as e.g. **3** and **4**, under various conditions. It may be used to particular advantage if the optical induction changes direction [7]. The (*S*)-enantioproductivity is doubled for the phenyl-*O*-glucoside chelate **4b** with an opened *m*-dioxane ring [$Q_S(\mathrm{OPh}) = q_S\mathbf{4b}/q_S\mathbf{3b} = 2.1 \pm 0.4$]. In the case of phenyl-*C*-glucoside chelate **4c** it is tripled [$Q_S(\mathrm{CPh}) = q_S\mathbf{4c}/q_S\mathbf{3c} = 3.0 \pm 0.7$]. However, the deviation from the average is less than a quarter of its value in both cases and does not show a distinct course in dependence on solvent polarity (see Experimental, Table 4).

The discussion of the results remains speculative at this point. Too little is known about the mechanism of hydrogenation with 7-membered ring chelates. If we assume the Halpern mechanism to be valid for our case (two diastereomer catalyst-substrate complexes – major and minor – possessing different reactivity in the rate determining step and thus determining the ratio of *S*- to *R*-enantiomer [15,16]) we wonder whether there may not be two or more major-minor couples for the different conformers present simultaneously. For the Ph-β-glup complexes, in accord with suggestions by Pavlov et al. [13] we have to assume first of all that the λ-chair conformation of the seven-membered chelate ring leads to (*S*)-amino acid derivatives. However, new results obtained by Habuš et al. [17] have shown that rhodium complexes of ligand **7** with the inverse configuration (*R*,*R*) also produce (*S*)-amino acids giving a high optical yield of more than 65% ee (*S*)-**2b**. This could originate in an unexpected λ-boat conformation for the 7-membered chelate ring [13]. We have attempted to prepare ligands similar to **7** but with an additional



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condensed ring in the expectation that the (*R*)-amino acid derivatives are the main hydrogenation products, owing to the preference for the δ-chair conformation in the catalyst chelate. The pure λ-boat conformation carrying axial $-OPPh_2$ groups should be extremely unfavoured in this case.

Some information about the influence of intramolecular hydrogen bridges on the conformation of the chelated ligand may be deduced from IR spectra, thus those of of **4b** and **4c** in CH_2Cl_2 ($3 \cdot 10^{-3}$ m) in the ν(OH)-region show some similarities to results obtained by Matsumoto [18] on phosphorus-free carbohydrates. The ν(OH) absorptions, 3496 and 3596 cm^{-1}, for **4b** indicate the existence of an equilibrium

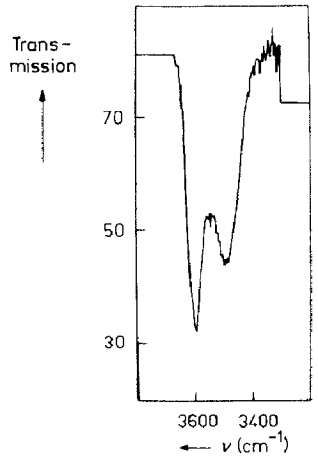
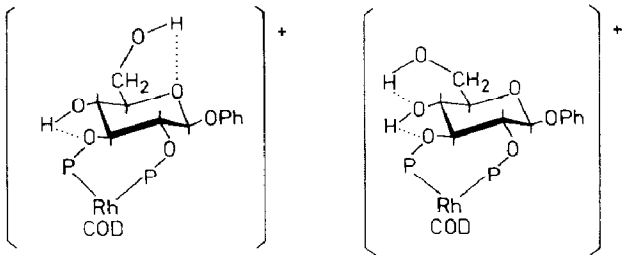


Fig. 2. IR spectrum of **4b** (3×10^{-3} *m*, CH_2Cl_2; *d* 1 cm).

between **4bα** and **4bβ** lacking the free CH_2OH group as deduced from the absence of an absorption at 3640 cm^{-1}. In the case of **4c** the situation is not so well defined: ν(OH) 3596 cm^{-1} shows only a shoulder at 3525 cm^{-1}. Hydrogenation measurements in many solvents were carried out in the expectation that they possessed varying abilities to form hydrogen bridges, so that a distinct deviation of the two catalyst groups **4** and **3** could be seen. However, despite the clear increase of Δ% ee (**4-3**) values (Table 2) with decreasing polarity of the solvent used there are doubts as to its importance if we compare the relevant *Q* values (Table 4). Thus, we cannot present definite reasons for the higher enantioselectivity of the hydrolyzed complexes **4** at the moment. It is probable that an unfavourable flattening of the suggested $^4C_1$-conformation of the glucopyranoside ring in the 4,6-*O*-alkylidene-protected chelates **3**, and particularly in nonpolar solvents, such as aromatic hydrocarbons, results in the unsuitable edge-face conformation of the phenyl phosphino groups *. This flattening may be partly compensated in polar solvents, such as alcohols and tetrahydrofuran, and can be reversed if the fixing *m*-dioxane ring is solvolysed. Extended NMR studies in different solvents should throw more light on this.



4bα 4bβ

* The importance of an edge-face conformation of the phenylphosphine groups in chiral complexes for enantioselectivity is described elsewhere [13,19–22].

The high enantioselectivity of the complexes **4** shows the importance of bulky equatorial substituents (e.g. R^1, OH and CH_2OH) in the pyranoside ring to the optical induction. Rhodium complexes of the ligands **5**, **6**, and **7** without such additional substituents gave poorer results.

We also attempted to find out whether the higher enantioselectivity of precatalysts **3a** or **3b** in the hydrogenation of acid substrates such as **1a** and **1b** (96.4 ± 1.0% ee, see Table 3) compared with the analogous esters **1c** and **1d** (91.5 ± 0.5% ee) in methanol is a property inherent to these catalysts with intact ligand, or whether it arises from the solvolysis of the acetal ring of the ligand under the catalytic action of the proton available from the acid substrates. Thus successive hydrogenations first with acid **1b** and then with ester **1c** have indicated that there is some solvolytic influence by the acid substrate **1b** (or product **2b**) on type **3** catalysts during the hydrogenation. Owing to the somewhat increased enantioselectivity estimated for the second ester substrate especially in the case of the more susceptible isopropylidene catalyst **3b** we conclude, that solvolysis of the acetal ring starts early in the hydrogenation of the acid **1b** but does not reach the end point. This means, that for substrate acids the high enantiomeric excess of 96.4 ± 1.0% ee (*S*)-**2a** (or -**2b**) is caused by the intact catalysts of type **3** themselves.

Experimental

All procedures used were as previously described [1]. For the successive hydrogenations of **1b** and **1c** (Table 3) 1 mmole **1b** was hydrogenated with 0.01 mmole precatalyst **3** in 15 ml methanol at 25°C and 0.1 MPa H_2. After 30 min of hydrogenation 1 mmole **1c** was added and then hydrogenated for a further 30 min.

All the investigated complexes **3** and **4** had BF_4^- as counterion. Their preparation has been described in [1].

For the distinction of the optical induction applying two variables (e.g. catalyst species, solvents, substrates etc.) the comparison of the differences of the enantiomeric excess Δ% ee) in two or more cases does not give a good idea of microscopic events. Thus, an increase of 5%, from 90 to 95% ee (*S*)-enantiomer, is equivalent to a doubling of the (S)-enantioproductivity ($q_S = S/R$ rises from 19 to 39). For such

Table 3

Hydrogenation of dehydro-phenylalanine derivatives (**1b** and **1d**) respectively alanine precursors (**1a** and **1c**) and experiments with successive hydrogenation of acid **1b** and ester **1c** (see text). (For conditiones see Table 1).

Complex	Substrate								
	1b		**1d**		**1a**		**1c**		**1c** (after hydrogenation of **1b**)
	t/2 min	% ee (*S*)-**2b**	*t*/2 min	% ee (*S*)-**2d**	*t*/2 min	% ee (*S*)-**2a**	*t*/2 min	% ee (*S*)-**2c**	% ee (*S*)-**2c**
3a	2	96.6	6	91.5	1	97.7	1	90.9	92.8
3b	4	95.4	5	91.3	1	96.8	2	92.2	94.2
4b	3	95.1	3	94.8	1	96.5	2	95.2	

Table 4

Comparison of the (*S*)-productivity q_S ($q_S = S/R = 1/q_R$) for the complexes **3** and **4** using the results of Table 2

solvent	q_S(**3a**)	q_S(**3b**)	q_S(**3c**)	q_S(**4b**)	q_S(**4c**)	Q_S(OPh) q_S(**4b**)/ q_S(**3b**)	Q_S(CPh) q_S(**4c**)/ q_S(**3c**)
MeOH	22.5	22.0	13.2	37.5	32.9	1.7	2.5
EtOH	22.5	25.3	14.3	46.6	36.0	1.8	2.5
i-PrOH	22.8	26.8	15.4	44.5	32.3	1.7	2.1
THF	13.4	14.3	9.0	35.4	29.8	2.5	3.3
dioxane	8.5	8.6	6.7	15.7	17.7	1.8	2.6
benzene	9.5	9.4	6.7	24.3	26.0	2.6	3.9
toluene	9.5	10.0	7.0	22.8	27.2	2.3	3.9

an increase an improvement by more than 30% ee is required, for ee's between viz., 20 and 50% (q_S rises from 1.5 to 3.0). Thus the q_S values of important measurements are also presented in Table 4.

Acknowledgements

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