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Studies on enantiotopic differentiation in the horse liver alcohol dehydrogenase catalysed reduction of chiral tricarbonyl-(η^6-benzaldehyde)chromium complexes

Clara Baldoli*,[a,*] Paola Del Buttero,[a] Stefano Maiorana,[a,†] Gianluca Ottolina*[b] and Sergio Riva[b]

[a]*Dipartimento di Chimica Organica e Industriale dell'Universita' e CNR Centro Studio Sintesi e Stereochimica Speciali Sistemi Organici, Via C. Golgi 19, 20133 Milano, Italy*

[b]*CNR Istituto di Chimica degli Ormoni, Via M. Bianco 9, 20131 Milano, Italy*

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Abstract

Horse liver alcohol dehydrogenase (HLADH) catalysed reduction of a series of *ortho*- and *meta*-substituted benzaldehyde chromium tricarbonyl complexes has been studied. The kinetic resolution proceeded with variable enantioselectivity and the extent of chiral discrimination strongly depended on the nature and the position of the substituent on the aromatic ring. Computer graphics were used to examine the docking of benzaldehyde complexes into the HLADH active site and to explain the different enantiopreference found along the *ortho* series.

1. Introduction

Enzymatic catalysis has been used as a method to solve relevant synthetic problems, particularly for the preparation of optically active fine chemicals. The use of enzymes has been greatly boosted by the discovery that these biocatalysts can also work in non-natural conditions, being active in organic solvents and transforming unusual substrates such as organometallics.[1] Several authors have widely reported on the application of lipases[2] and reductases[3] to the resolution of various chiral organometallic compounds. Specifically, in a previous paper we have described the enantioselective reduction of some tricarbonyl chromium benzaldehyde complexes by baker's yeast.[3c] This method has been one of the first examples of bioconversion applied to arene chromium tricarbonyl complexes[3b,c] and in some cases can be used as an inexpensive way to prepare optically active complexes. In the yeast catalysed reduction of *ortho*-

* Corresponding author.

† E-mail: maior@icil64.cilea.it

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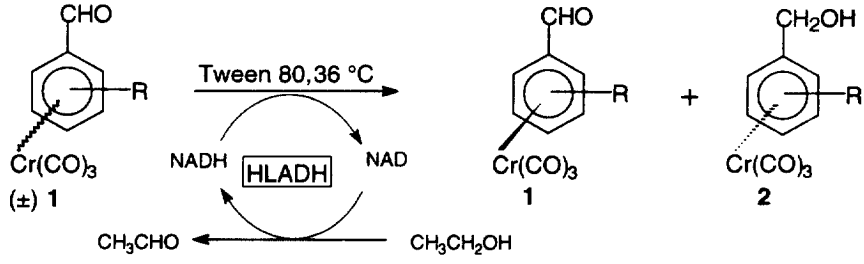
and *meta*-substituted benzaldehyde complexes we noted a dependence of the e.e. on the nature and the position of the substituent on the aromatic ring. The inversion of configuration of the major enantiomer on passing from the *ortho* to the *meta* series was noteworthy, and the stereochemical outcome was rationalised in terms of Prelog's rule.[4]

Since yeast is a microorganism containing a number of different oxidoreductases, the enzyme responsible for the catalytic reduction cannot be identified, thus hindering further speculations on the nature of the substrate interaction with the active site of the biocatalyst. Aiming to extend our studies on the enzymatic resolution of benzaldehyde complexes, we turned our attention to a definite oxidoreductase, i.e. the alcohol dehydrogenase from horse liver (HLADH), which has been widely used for the resolution of several ketones and alcohols.[5] Moreover, some models for the active site of HLADH have been proposed to explain or to predict the specificity of this enzyme with different substrates.[6]

Yamazaky has reported some interesting studies on HLADH catalysed oxidoreduction of organometallic species. Various iron and manganese derivatives have been extensively investigated, but only 2-methyl benzaldehyde has been studied among arene chromium tricarbonyl complexes.[3d,e]

Thus, to collect more data on HLADH specificity with these organometallics, we decided to investigate the stereochemical course of the HLADH catalysed reduction of a series of *ortho*- and *meta*-substituted tricarbonyl(η^6-benzaldehyde)chromium complexes **1a–h** (Scheme 1).



R, **a**: 2-CH_3 **e**: 3-CH_3
b: 2-Cl **f**: 3-Cl
c: 2-OCH_3 **g**: 3-OCH_3
d: 2-F **h**: 3-F

Scheme 1.

2. Results and discussion

The reduction was performed in aqueous phosphate buffer solution in the presence of Tween 80®, as surfactant, and ethanol (used both as a second substrate for cofactor regeneration and as cosolvent to solubilise the benzaldehyde complexes). We introduced some modifications with respect to the experimental conditions reported by Yamazaky,[3d] i.e. we increased the reaction temperature to avoid the precipitation of the complexes and we used a smaller amount of enzyme. In this case the aldehyde complexes were solubilised in the aqueous mixture at 55°C, and HLADH/NAD was added after cooling to about 36°C.

All reactions were run at 36°C, monitored by HPLC on a silica gel column, and stopped at about 50% conversion.[7] Complexes **1a–h** and **2a–h** were recovered by flash-chromatography in good yield and their enantiomeric excesses were determined by chiral HPLC (Table 1).

Table 1

Substrate	Reaction	HPLC ratio	Unreduced 1			Alcohol 2		
(±)-1	time (h)	1 : 2	y %[a]	e.e.%[b]	Config.[c]	y %[a]	e.e%[d]	Config.
ortho								
a	8	52 : 48	98	81[e]	*S*	69	91	*R*
b	7	46 : 54	67	47[e]	*S*	97	58	*R*
c	6.5	49 : 51	97	19	*R*	91	23	*S*
d	5	56 : 44	72	22	*R*	79	19	*S*
meta								
e	2.5	50 : 50	98	48	*S*	70	60	*R*
f	3	48 . 52	87	60[e]	*S*	98	56	*R*
g	5	51 : 49	80	30	*S*	72	21	*R*
h	7.5	41 : 59	85	7	*S*	62	4	*R*

a: Determined on isolated products
b: Determined by chiral HPLC after reduction to alcohol with $NaBH_4$ [8]
c: $[\alpha]_D$ are reported in ref. 10.
d: Determined by chiral HPLC
e: Determined by ^1H NMR with $Eu(hfc)_3$

Considering the *ortho*-substituted substrates, the most remarkable data shown in Table 1 concern the decrease of chiral discrimination on passing from methyl to other substituents. The best enantiomeric ratio was achieved with the *ortho*-methyl benzaldehyde complex **1a**. As mentioned before, this substrate had already been tested by Yamazaky,[3d] but for the sake of comparison, **1a** was also reacted under our experimental conditions. We recovered the aldehyde **1a** in 81% e.e. and the corresponding alcohol **2a** in 91% e.e. (the Japanese authors had found 97% e.e. for both **1a** and **2a**, running the reaction at 5°C). On the other hand, the e.e. was particularly low in the case of *ortho*-methoxybenzaldehyde **1c**, whereas this substrate had given a rather good selectivity in kinetic resolution with baker's yeast. Moreover, the most surprising result was the inversion in the enantiopreference of HLADH on passing from 2-CH_3 and 2-Cl [(1*S*) configuration for the unreduced **1a** and **1b**] to 2-OCH_3 and 2-F-substituted benzaldehyde complex [(1*R*) configuration for unreacted **1c** and **1d**].

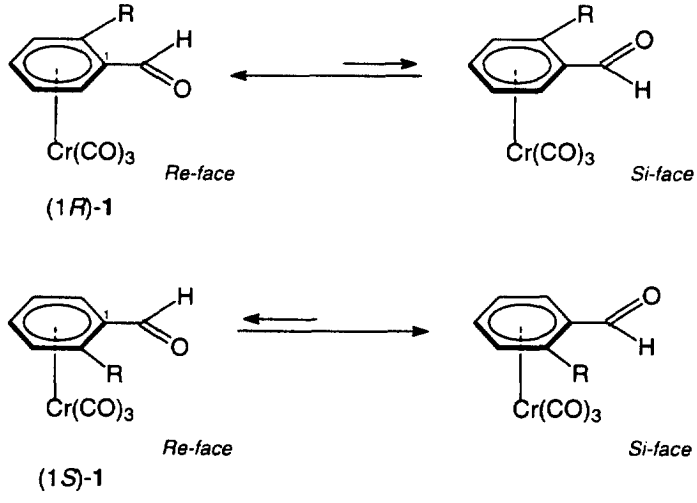
Along the *meta* series, a very low enantioselectivity was again found for the OCH_3-substituted complex **1g** with respect to that of 3-CH_3 and 3-Cl complexes **1e** and **1f**, while almost no discrimination was found with the 3-F benzaldehyde complex. Nevertheless, the absolute configuration was (1*S*) for all of the unreduced *meta*-substituted benzaldehyde complexes, as ascertained by comparison of their CD curves which showed a positive Cotton effect at about 320 nm in CH_2Cl_2 solution.[9,10]

Except for the 2-CH_3 benzaldehyde complex **1a**, HLADH seemed to be a slightly less efficient catalyst than baker's yeast. However, the observed change in the enantiopreference of this enzyme along the *ortho* series was a particularly intriguing result, that prompted us to search for an explanation of this selectivity on the basis of the known models of this protein's active site.[6]

Some years ago, Jones proposed a cubic space model for predicting and interpreting the specificity of PLE and HLADH with many different substrates.[6a] This active site model has been recently adopted to elucidate the selectivity displayed by PLE in the resolution of (benzene-1,2-diacetic esters)–$Cr(CO)_3$

complexes.[2a] However, since in the meantime the 3D structure of HLADH[11] has been elucidated, it is now possible to investigate the interaction of the substrate with the enzyme active site by directly studying the molecular docking. Accordingly, to explain the observed different specificity we decided to use computer graphics to examine the docking of *ortho*-substituted aldehyde complexes **1a–d** into the 3D structure of the active site of HLADH.

Prior to discussing in more detail the docking of the complex into the active site, we have to consider the carbonyl face selectivity. Previous papers ascertained, through experiments on deuterated substrates, that in different organometallics the reduction of the carbonyl group, catalysed by yeast or HLADH, proceeds with a *Re*-face selectivity.[3c–e] Since no *ortho*-substituted complexes have been tested in such experiments, for the sake of completion we ran the HLADH catalysed reduction of 2-methyl benzaldehyde–$Cr(CO)_3$ **1a** in the presence of deuterated ethanol (see Experimental). The alcohol thus obtained had an *R* configuration at the deuterated benzylic carbon atom[12,13] and this result shows that the hydride addition also occurs on the *Re*-face of the carbonyl for **1a**. As previously discussed[3c] the enzyme mediated hydride attack should take place from the upper side of the ring (on the opposite side to the $Cr(CO)_3$ group) on the carbonyl group '*anti*' to the *ortho*-substituent.[11] This assumption well accounted for the preferential reduction of the (1*R*) enantiomer of *ortho*-complexes **1a,b** in which the *Re*-face of the CO is both the favourite and more accessible conformation (Scheme 2).



Scheme 2.

On the other hand, the reduction of the (1*S*) enantiomer for **1c,d** (in which the *Si*-face is the favourite conformation), shows that in some cases the enzymatic mechanism acts on the substrate through different specific interactions. We therefore resorted to computer graphics to try to explain the substrate–enzyme interaction along the *ortho* series. For the construction of the active site we used the structure of a tertiary complex of HLADH, bound to NAD and *para*-bromobenzyl alcohol, derived from the Brookhaven protein database.[14] The chromium tricarbonyl complex was built according to the crystallographic data obtained for tricarbonyl(η^6-toluene)chromium[15] and was docked into the cavity replacing the original alcohol.

We considered as model compounds *ortho*-methyl- and *ortho*-methoxybenzaldehyde chromium tricarbonyl complexes **1a** and **1c**, which showed opposite enantioselectivity in the course of the reduction [namely (1*S*) configuration for the recovered **1a** and (1*R*) for **1c**].

The formyl group of both (1*R*)- and (1*S*)-enantiomers of **1a** and **1c** was placed at the reaction site turning the *Re*-face towards the coenzyme. A simple rotation along the Zn–O bond positioned the

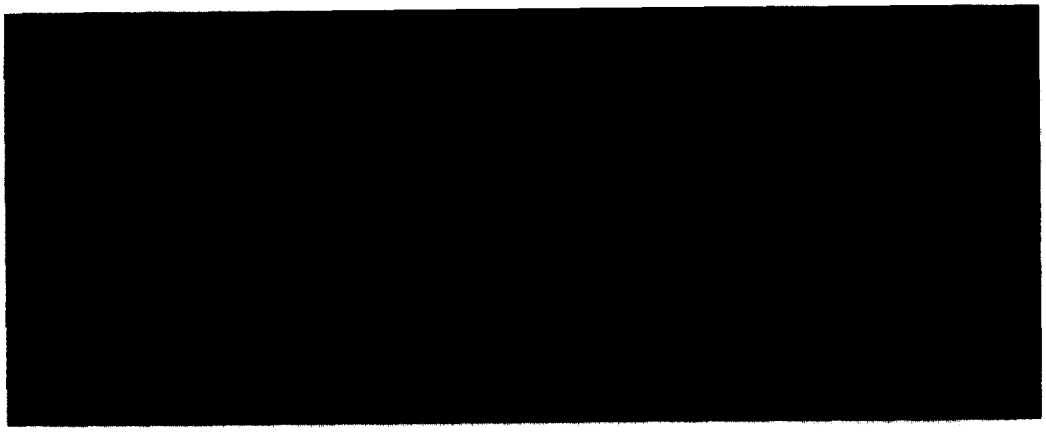


Fig. 1. Docking of (1*R*)- and (1*S*)-2-methylbenzaldehyde–$Cr(CO)_3$ **1a** into the HLADH active site

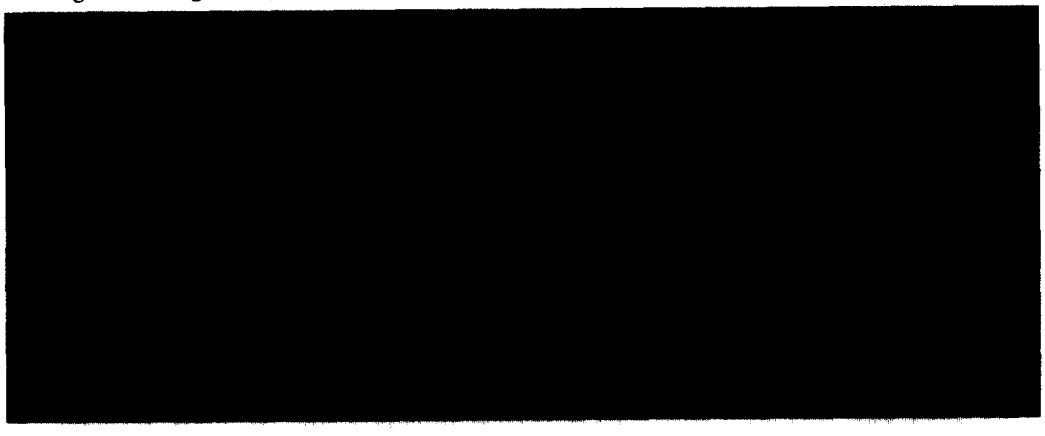


Fig. 2. Docking of (1*R*)- and (1*S*)-2-methoxybenzaldehyde–$Cr(CO)_3$ **1c** into the HLADH active site

complex into a suitable orientation and distance for the direct hydrogen transfer from the cofactor. The models reported in Figs 1 and 2 represent the situation after the hydrogen transfer from HLADH to the carbonyl.

We first examined the case of 2-methylbenzaldehyde complex **1a** (Fig. 1). As shown in Fig. 1 (left), the (1*R*)-enantiomer is better accommodated in the cavity, due to the fact that the *ortho*-methyl group points towards an empty space, without significant steric interaction with surrounding residues of Phe93, Thr94 and Ile314. In contrast, the docking of the (1*S*)-enantiomer of **1a** (Fig. 1, right) shows that the methyl group comes close to the hydroxy group of Ser48 disturbing its hydrogen bond with the carbonyl oxygen which is necessary for the catalysis. In a similar way it is possible to explain the same selectivity observed with the 2-chlorobenzaldeyde complex **1b**.

As already mentioned, a reverse selectivity (although with a very low e.e.) was observed with 2-methoxy and 2-fluorobenzaldehyde complexes **1c** and **1d**. As shown in Fig. 2 (right) the accommodation of the (1*S*)-enantiomer of 2-methoxybenzaldehyde **1c** inside the active site probably causes only minor disturbance to the hydrogen bond between Ser48 and the oxygen bonded to Zn. In fact the angular geometry of the methoxy group keep the methyl group far away, leaving only its oxygen close to Ser48. In the same way the negligible steric hindrance of the fluorine makes possible the accommodation of the (1*S*)-enantiomer of 2-fluorobenzaldehyde **1d**. Additionally, a possible explanation for the preferential accommodation of the (1*S*)-enantiomer in **1c** and **1d** could be found in the hydrogen bond stabilisation of the *ortho*-substituent, since both methoxy and fluorine[16] can act as hydrogen bond acceptors towards

the OH group of Ser48. However the enantiomeric excesses obtained with **1c** and **1d** were quite low indicating that although the (1*S*)-alcohols were the major products, a discrete amount of (1*R*)-substrate binds the enzyme with the *ortho*-substituent pointing in the usual empty space surrounded by the Phe93, Thr94 and Ile314 (Fig. 2, left).

In conclusion, despite the fact that HLADH selectivity towards most of the substrates investigated in this work is worse than the selectivity obtained with baker's yeast, the use of this pure enzyme allows a more accurate rationalisation of the results. Specifically the use of computer graphics to examine the positioning of the benzaldehyde complex inside the active site, seems to afford a reasonable interpretation for the opposite enantiopreference shown by HLADH in the reduction of *ortho*-substituted benzaldehyde complexes **1a** and **1b**, and **1c** and **1d**.

3. Experimental

NMR spectra were recorded on a Bruker AC 300 spectrometer. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. All benzaldehyde–$Cr(CO)_3$ complexes were prepared according to a standard procedure.[3c] HLADH and NAD were purchesed from Sigma–Aldrich.

3.1. Tricarbonyl(η^6-3-chlorobenzaldehyde)chromium ***1f***

A deoxygenated mixture of $Cr(CO)_6$ (1 g, 0.46 mmol), 3-chlorobenzaldehyde diethyl acetal (0.75 g, 0.35 mmol), dioxane (20 ml) and THF (5 ml) was heated at about 90°C for 10 hours. The solution was then evaporated under reduced pressure, the residue was taken up with diethyl ether (10 ml) and filtered over Celite. After evaporation of the solvent, the crude yellow residue was diluted with dioxane (10 ml) and treated with 3 M HCl (1.2 ml). The solution was stirred for 1 hour at room temperature, treated with a saturated solution of $NaHCO_3$ (30 ml) and extracted with Et_2O (3×20 ml). The organic extracts were combined, washed with H_2O (20 ml), dried (Na_2SO_4) and evaporated to give a red oil. Column chromatography on silica gel (eluent: petroleum ether:diethyl ether=3:1) afforded complex **1f** in 56% yield as red crystals, m.p. 53–55°C (petroleum ether).[17] ^{1}H NMR ($CDCl_3$, δ): 5.4 (pt, 1H, J=6.5 Hz, J=6.3 Hz); 5.7 (d, 1H, J=6.3 Hz); 5.8 (d, 1H, J=6.5 Hz); 6.0 (bs, 1H); 9.5 (s, 1H, CHO).

3.2. Tricarbonyl(η^6-3-fluorobenzaldehyde)chromium ***1h***

Compound **1h** was obtained following the same procedure used for **1f**. Yield 38%. ^{1}H NMR ($CDCl_3$, δ): 5.4–5.5 (m, 2H); 5.7 (bs, 1H); 5.9 (d, 1H, J=3.4 Hz); 9.6 (s, 1H, CHO). Anal. calc. for $C_{10}H_5FCrO_4$: C, 46.76; H, 1.94. Found: C, 46.36; H, 1.95.

3.3. Enzymatic reduction

The general procedure used for the reduction is as follows: A mixture of 0.1 M phosphate buffer pH 7.5 (20 ml) and Tween 80® (1.2 ml) was heated to 55°C. Racemic benzaldehyde complex **1a–h** (100 mg), previously dissolved in EtOH (2.2 ml) was added to this solution with stirring. The mixture was heated until the complete solubilisation of the complex was observed. After cooling to about 36°C, HLADH/NAD (8–10 mg of NAD and 20–30 U of HLADH were used for complexes **1a–d**; 4–6 mg of NAD and 5–10 U of HLADH for **1e–h**) was added and the mixture was shaken at the same temperature for the appropriate time. The reaction was followed by HPLC (eluent: hexane:ethyl

acetate=1:1). The mixture was diluted with MeOH (100 ml) and the solvent evaporated under reduced pressure. This procedure was repeated until the water was removed. The residue was then purified by flash chromatography using AcOEt:CH_2Cl_2 (1:1) as eluent.

3.4. Enzymatic reduction of tricarbonyl(η^6-2-methylbenzaldehyde)chromium with ethanol-d_6

A solution of 2-methylbenzaldehyde–$Cr(CO)_3$ (200 mg) in C_2D_5OD (4.4 ml) was added to a mixture of 0.1 M phosphate buffer pH 7.5 (40 ml), previously heated at 55°C. The mixture was heated at the same temperature until the complete dissolution of the complex. After cooling to 37°C, NAD (15 mg) and HLADH (45 U) were added and the solution was shaken for 10 hours. After the same work-up as reported in the general procedure, deuterated benzyl alcohol was recovered as a yellow solid in 90% e.e. M.p. 96–98°C (pentane). ^1H NMR ($CDCl_3$, δ): 1.8 (bs, 1H, OH); 2.2 (s, 3H, CH_3); 4.4 (bs, 1H, CH); 5.19–5.24 (m, 2H, arom); 5.38 (pt, 1H, J=6.3 Hz, arom); 5.6 (d, 1H, J=6.3 Hz). $[\alpha]_D$=−9.3, (c=0.2, $CHCl_3$).

3.5. Determination of ε for complexes 1 and 2

A JASCO V-350 spectrophotometer was used to measure the ε values of complexes **1** and **2**, which were determined using 10^{-5} M CH_2Cl_2 solutions.

R	λ(nμ)	ε	
		1	2
a: 2-CH_3	318	8360	8359
b: 2-Cl	320	8744	10006
c: 2-OCH_3	314	7067	8677
d: 2-F	314	6776	9489
e: 3-CH_3	316	7147	8241
f: 3-Cl	320	6638	8300
g: 3-OCH_3	316	5799	6081
h: 3-F	314	6208	9281

3.6. HPLC analysis

HPLC analyses were performed using a Jasco HPLC instrument (model 880-PU pump, model 870-UV detector). The reduction was followed using a silica gel column, (eluent: hexane:ethyl acetate=1:1); flow rate 0.8 ml/min, reading at the appropriate λ for **1** and **2** (see above).

The e.e.s of complexes **2a–h** were determined using a 10 μm Baker Bond Chiracel OD column, for **2a–e** and **2g** (eluent: hexane:isopropanol=9:1), flow rate 0.5 ml/min.; for **2f** and **2h** (eluent: hexane:ethanol=98:2), flow rate 0.5 ml/min.

Acknowledgements

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7. To ensure an accurate evaluation of the degree of conversion, we measured the ε values for all benzaldehyde and benzyl alcohols complexes (see Experimental).
8. This was due to the fact that benzaldehyde complexes were retained on the stationary phase of chiral HPLC column.
9. The CD spectra of compounds **1e–h**, measured using a 10^{-5} CH_2Cl_2 solution, gave a positive Cotton effect for the n–π^* transition with an extremum at λ=323 (Δε=+3250) for **1e**, λ=324 (Δε=+2371) for **1f**, λ=322 (Δε=+1030) for **1g** and λ=315 (Δε=+210) for **1h**.
10. $[\alpha]_D$ of all benzaldehyde complexes **1a–g** were determined in $CHCl_3$ solution (c=0.02): **1a**, $[\alpha]_D$=+510; **1b**, $[\alpha]_D$=+473; **1c**, $[\alpha]_D$=−225; **1d**, $[\alpha]_D$=−240; **1e**, $[\alpha]_D$=−126; **1f**, $[\alpha]_D$=−160; **1g**, $[\alpha]_D$=−206; $[\alpha]_D$ of the optically pure complexes **1a–e** and **1g** are reported in Ref. 3c. Compound **1f** is not known in enantiomerically pure form.
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12. The value and the sign of the specific rotation ($[\alpha]_D$=−9.3) of deuterated benzylalcohol obtained from enzymatic reduction of racemic **1a** was compared with that ($[\alpha]_D$=−11) of the alcohol obtained from the reduction of the (1*R*) enantiomer of **1a** using $NaBD_4$. In fact it is known that for the (1*R*) enantiomer of *ortho*-substituted benzaldehyde complexes the attack of the nucleophile usually occurs on the *Re* face of the carbonyl.[13]
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