Enantioselective Microbial Reduction of Planar Chiral Organometallics of Synthetic Interest

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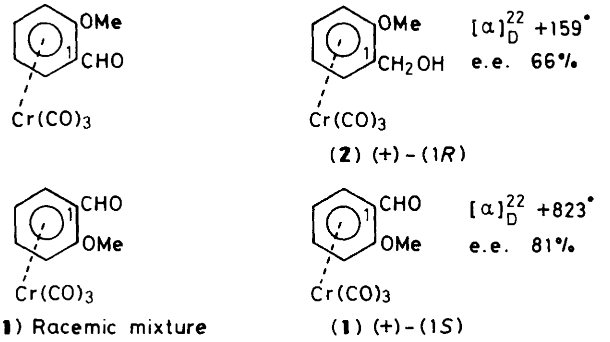
Reduction of racemic tricarbonyl(2-methoxybenzaldehyde)chromium with baker's yeast allows the ready preparation of the planar chiral alcohol and aldehyde complexes in optically active forms.

The synthetic opportunities provided by enzymes as specific and chiral catalysts have been recently developed into biochemical procedures with experimental techniques which are also acceptable in organic synthesis.[1] In this field the most useful enzymes are those which accept a rather broad range of substrates, while maintaining their ability to perform stereospecific reactions under mild conditions.

Therefore we thought that it could be of interest to combine the higher efficiency of enzymic catalysis with the unique structural features of planar chiral metallocenes, with the aim of facilitating the preparation of optically active organometallic synthons.

Here we report the first example of enantioselective microbial kinetic resolution of planar chiral metallocenic



Scheme 1. Enantioselective reduction of (**1**) by baker's yeast.

aldehydes which are of synthetic interest.[2] Recently Sokolov *et al.* reported a microbial reduction of ferrocene derivatives, but it was not a kinetic resolution.[3] Enantioselective reduction of the racemic mixture of tricarbonyl(2-methoxybenzaldehyde)chromium (**1**) by baker's yeast at 22 °C in water, in the presence of D-glucose, afforded (+)-(1*R*)-tricarbonyl(2-methoxybenzyl alcohol)chromium (**2**) in 66% enantiomeric excess (e.e.) and the optically active unchanged (+)-(1*S*)-enantiomer of tricarbonyl(2-methoxybenzaldehyde)chromium in 81% e.e. (Scheme 1).

The usefulness of optically active arenetricarbonylchromium species in asymmetric synthesis is now well established, but in these series certain functions such as aldehyde and alcohol remain rather difficult to obtain rapidly in sufficiently high enantiomeric excess.[4,5] The reaction was carried out by adding a solution of racemic (**1**) (109 mg, 0.4 mmol) in ethanol (5 ml) to a previously prepared baker's yeast suspension.† Reaction progress was monitored by h.p.l.c. analysis‡ and was stopped after 6 h (55% conversion). Extraction of the mixture with Et$_2$O afforded crude product (108 mg, 99%), which was purified by preparative chromatography on a silica gel plate [eluant Et$_2$O–pentane (2:1)]. (+)-(1*S*)-tricarbonyl(2-methoxybenzaldehyde)chromium (49 mg) was isolated as a red solid, $[\alpha]_D^{22}$ +823° (CHCl$_3$, *c* 0.43), e.e. = 81% and (+)-(1*R*) tricarbonyl(2-methoxybenzyl alcohol) chromium (52 mg) as a yellow solid, $[\alpha]_D^{22}$ +159° (CHCl$_3$, *c* 0.81), e.e. = 66%.§

The 81% e.e. obtained for (+)-(1*S*)-tricarbonyl(2-methoxybenzaldehyde)chromium can probably be improved by optimization of the reaction conditions or more simply by recrystallization. These preliminary results show that the complexation of an arene ring with the Cr(CO)$_3$ unit does not hinder the penetration of the complex into the yeast's cells and its reduction. The two enantiomers of the complex are not reduced at the same rate since the yeast operates a large discrimination depending on the configuration of the planar chiral molecule.

We have thus demonstrated how the rapidly developing area of enzymic catalysis can be combined with organometallic chemistry as a promising tool for the synthesis of a series of chiral metallocenic synthons.

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† Fresh baker's yeast (10 g) was stirred with demineralized water (100 ml) and the mixture was centrifuged for 10 min at 2500 rev min^{-1}. After removal of the water the washing procedure was repeated once again. Baker's yeast so treated was suspended in demineralized water (100 ml) and after addition of glucose (2.5 g) the mixture was stirred at room temperature (22 °C) for 30 min.

‡ Carried out on a Beckman 'Gold System' equipped with an octadecylsilane column; eluant methanol–water (70:30), flow 0.7 ml min^{-1}.

§ Enantiomeric excesses were established on the basis of maximum optical rotations reported in the literature[5,6] and the absolute configurations were determined by the method of Jaouen *et al.*[4]