Enantioselective Microbial Reduction of Transition-metal-complexed Aromatic Ketones

Jeannine Gillois,[a] Didier Buisson,[b] Robert Azerad,[b] and Gérard Jaouen[a]*

[a] *U.A. 403, E.N.S.C.P., 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France*
[b] *U.A. 400, Université R. Descartes, 45 rue des Saints Pères, 75270 Paris Cedex 06, France*

Several examples of reduction of $Cr(CO_3)$-complexed aromatic ketones by baker's yeast show that, in some instances, this methodology improves the velocity of reduction, increases enantiomeric excess, and even allows kinetic resolution of planar chiral complexes.

Two rapidly developing areas in modern organic synthesis involve the use of organometallic complexes[1] and of enzymic catalysts[2] in the preparation of chiral synthons. Examples combining these two methodologies are still rare,[3,4] and so far limited to the ferrocene series, the synthetic interest of which [unlike that of (arene)$Cr(CO)_3$ complexes], is not significant. We report here preliminary results concerning the reduction of (aryl ketone)$Cr(CO)_3$ complexes (**1**)—(**3**) by baker's yeast, which show the potential of this approach.

The bioreduction of acetophenone (free ligand) has already been described;[5—7] the (*S*)-alcohol is always obtained preferentially indicating that the reduction follows the so-called Prelog rule (Scheme 1; the large substituent L represents the aromatic group). However, chemical yield (20—39%) and enantiomeric excess (e.e. 55—60%) are low. Though other micro-organisms have been used,[8] only slightly higher yields have been obtained.

In this context we considered that the ready complexation[9] of arenes by $Cr(CO)_3$, followed by microbiological reduction and decomplexation with sunlight in air,[1a] might improve the yield and enantioselectivity of the reduction. Moreover, *ortho*- or *meta*-substituted phenyl ketone or cyclic ketone complexes such as (**3**) exhibit planar chirality and an enantioselective reduction of racemic mixtures, leading to resolution, is conceivable. To our knowledge, no example of such a resolution of an organometallic chiral complex has been described.

Compounds (**1**)—(**3**) were easily prepared in 90% yield according to the method of Pauson and Mahaffy[9] and reduced to the corresponding alcohols in the following way. Baker's yeast (16 g) was washed in water, centrifuged twice, dispersed into an aqueous solution of glucose (5 g in 160 ml of water), and preincubated with shaking for 1 h at 30 °C; the substrate (4 mmol), dissolved in ethanol (2 ml), was then added. After 1—7 days incubation, the suspension was extracted with diethyl ether–ethyl acetate (1 : 1 v/v) and the solvent was evaporated off under reduced pressure. The residue was dissolved in the minimum volume of cyclohexane–ethyl acetate (7 : 3) and purified by column chromatography on silica gel. The enantiomeric excess of the alcohol was determined, after photochemical oxidation in air and derivatization with isopropyl isocyanate,[10] by g.l.c. on a chiral capillary column [Chrompack XE-60 (*S*)-valine-(*S*)-α-phenylethylamide, 25 m × 0.25 mm].

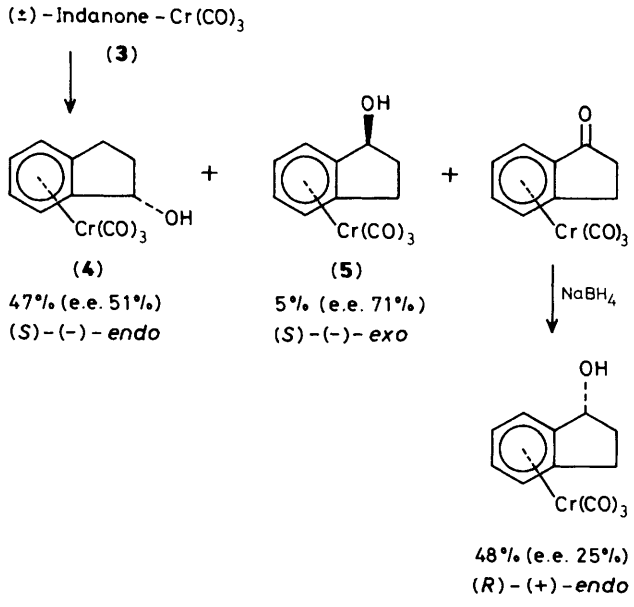
The acetophenone complex (**1**) is completely reduced in 24 h; the chemical yield, after purification, is 96% and the enantiomeric excess of the (*S*)-1-phenylethanol is higher than 99%. Under the same conditions, the free ligand gives the (*S*)-alcohol in 69% yield after 7 days reaction, with an optical purity of only 92%.

With the more bulky propiophenone complex (**2**), the reduction was very slow: after 2 weeks, only a 20% yield of the alcohol was formed. In contrast, free propiophenone is 50% reduced in 6 days. In both cases, the enantiomeric excess of the (*S*)-alcohol was 87%.

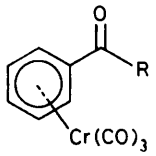
Bulk of the arene complex is an important factor to consider for the efficiency of the reduction. For example, substitution either at the benzene ring as in (2′,4′,6′-trimethylacetophenone)$Cr(CO_3)$ or at the tripod unit as in (acetophenone)-$Cr(CO)_2PPh_3$ sufficies to inhibit the reaction.

Reduction of (indanone)$Cr(CO)_3$ (**3**) (Scheme 2) gave a mixture of alcohols (*S*)-*endo*-(**4**) (47%) and (*S*)-*exo*-(**5**) (5%) with 51% and 71% optical purities, respectively. The recovered (+)-ketone (48%) showed 25% enantiomeric excess, estimated after reduction with sodium borohydride to

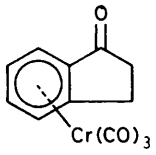
Scheme 1



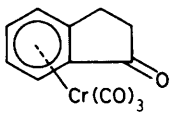
Scheme 2



(**1**) R = Me
(**2**) R = Et



(+)-(**3**)



(+)-(**3**)

endo-(indanol)$Cr(CO)_3$,† followed by decomplexation, formation of the corresponding isopropyl carbamate and g.l.c. on the chiral column.

From these results the following conclusions can be drawn.

(i) Complexation of an arene ring with the $Cr(CO)_3$ unit does not hinder penetration of the molecule into the yeast cells, and subsequent reduction of a carbonyl group, provided that the adjacent alkyl chain is not too bulky. The observed reducing capablity of yeast was unexpected, since it has been reported that sterically hindered ketones (*e.g.* t-butyl methyl ketone) are not reduced in this way.[5]

(ii) Indeed, the electron-withdrawing effect of the $Cr(CO)_3$ group makes bioconversion much faster for (**1**) and (**3**) with respect to the free ligands. These results are in agreement with observations made by several authors[6,7,12] concerning the reduction of acetophenones substituted by an electron-withdrawing group (*p*-NO_2, *p*-Cl, *p*-Br, or *p*-I).

(iii) The optical purity of the alcohol obtained from (**1**) is higher than that of the alcohol obtained from the uncomplexed ketone, probably as a consequence of the presence of a more sterically hindered substituent (Prelog's rule).

(iv) The enantiomers of (**3**) are not reduced at the same rate; this allows the first partial kinetic resolution of a planar chiral ketone complex. Reduction gives preferentially the *endo*-(indan-1-ol)$Cr(CO)_3$, corresponding to *exo*-attack of the hydride.

† As a result of the exclusive reduction to the *endo*-isomer,[11] the enantiomeric excess of the residual ketone is identical with the enantiomeric excess of the indanol obtained after decomplexation.

Additional work is in progress for the reduction of other complexes with various micro-organisms.

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