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KINETIC RESOLUTION OF CHIRAL METALLOCENIC ALDEHYDES AND ALCOHOLS WITH LIVER ALCOHOL DEHYDROGENASE

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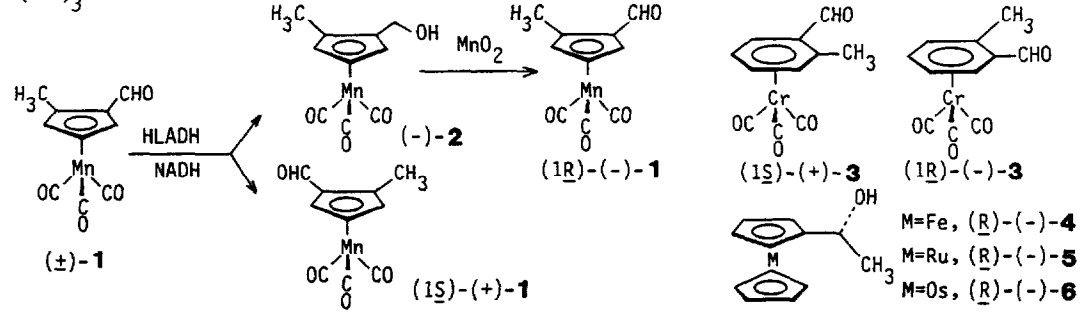
Summary: Horse liver alcohol dehydrogenase-catalyzed oxidoreduction was useful to resolve racemic 1-formyl-2-methyl derivatives of tricarbonyl(cyclopentadienyl)manganese and (benzene)tricarbonylchromium and racemic 1-hydroxyethylferrocene, ruthenocene and osmocene.

Enzyme-mediated asymmetric transformation is a useful method to prepare optically active organometallic compounds, as recently shown by us with horse liver alcohol dehydrogenase (HLADH) for ferrocene derivatives[1a] and several other groups with hydrolases for 1-ferrocenylethanol,[1b,c] a dienoate-iron complex,[1d] or silicon-containing esters.[1e] Microbial reductions of aromatic ketones and aldehydes complexed with $Cr(CO)_3$ have been also reported.[1f~h] Here we describe how *HLADH is useful* in the bioconversion of more various organometallic compounds.

(±)-Tricarbonyl(η^5-1-formyl-2-methylcyclopentadienyl)manganese (1,[2] 118 mg) was reduced with HLADH (120 U as assayed with EtOH) and NADH at pH 7.5 and 4°C.[3] When the TLC monitor showed that the spots for 1 and the product 2 had almost the same size at 2.5 hr, the compounds were extracted with EtOAc and isolated by silica gel column chromatography as optically active oils: 1 (36 mg, 31 % yield), $[\alpha]_D^{26}$+101°(c=2.2, benzene); and 2 (41 mg, 35 % yield), $[\alpha]_D^{25}$-8.7°(c=2.1, benzene).[4] The latter was oxidized with MnO_2 to give the levorotatory aldehyde 1 in 78 % yield, $[\alpha]_D^{23}$-104°(c=2.1, benzene). The absolute configuration of (+)-1 was determined to be (1S, 2R) by its oxidation with Ag_2O to the known (1S)-(+)-tricarbonyl(η^5-1-carboxy-2-methylcyclopentadienyl)manganese (76 % yield, mp 148~149°C, $[\alpha]_D^{25}$+84°(c=0.50, EtOH); lit.[5] mp 145~148°C, $[\alpha]_D$+83.3°(c=1.0, EtOH)).

(±)-Tricarbonyl(η^6-2-methylbenzaldehyde)chromium (3)[6] was also resolved by the HLADH-catalyzed reduction to (1S)-(+)-3 (28 % yield, mp 94~95°C, $[\alpha]_D^{25}$+654°(c=0.20, $CHCl_3$); lit. mp 99~100°C,[7] $[\alpha]_D^{20}$+665°(c=0.3, $CHCl_3$)[8]) and (1R)-(-)-3 (mp 96~97°C, $[\alpha]_D^{25}$-659°(c=0.20, $CHCl_3$)) via DMSO-Ac_2O oxidation of the enzymically produced 2-methylbenzyl alcohol complex (36 % yield, mp 97~98°C, $[\alpha]_D^{25}$-12°(c=1.9, benzene)). The enantiomeric purity was almost 100 %e.e. for all aldehydes ((+)- and (-)-1 and 3), as evidenced by the single aldehyde proton signal in the PMR spectrum measured with $Eu(hfc)_3$.[8]



(±)-1-Hydroxyethylferrocene (4), ruthenocene (5) and osmocene (6) were enantioselectively oxidized with HLADH, NAD^+ and FMN[9] to give the ketones and levorotatory alcohols: (-)-4, 44 % yield, mp 76~77°C, $[\alpha]_D^{29}$ -29°(c=0.51, benzene) (lit.[10] mp 72~73°C, $[\alpha]_D^{25}$ -30.5°(c=1.1, benzene)); (-)-5, 44 % yield, mp 77~78°C, $[\alpha]_D^{23}$ -21°(c=2.0, benzene) (lit.[11] $[\alpha]_D^{25}$ +20.7°(c=1.5, benzene)); and (-)-6, 33 % yield, mp 90~91°C, $[\alpha]_D^{23}$ -15°(c=2.0, benzene). HPLC analysis with a β-cyclodextrin-bonded column[12] indicated that the enantiomeric purity was 100 % e.e. for (-)-4 (with no detectable antipode peak) and 92 ± 1 %e.e. for (-)-5 and (-)-6.[13]

The present enzymatic resolution method is very facile, as it needs neither derivatization such as the semioxamazone formation used for 3[7] nor temporary conversion to amine or carboxylic acid.[11,14] Jaouen et al.[1g] resolved an organometallic aldehyde resembling 3 by baker's yeast reduction, but the present HLADH method is more promising for high enantiomeric purity and experimental convenience.

References and Notes

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3. 1 was dissolved in the medium (60 ml of 0.1 M phosphate buffer, pH 7.5, containing 2 % EtOH and 2.5 % Tween 80) by sonication before addition of HLADH and NADH (85 μmol).

4. MS for (+)-1 m/z: 245.9717 (M^+); calc. $C_{10}H_7MnO_4$=245.9725. MS for (-)-2 m/z: 247.9960 (M^+); calc. $C_{10}H_9MnO_4$=247.9881. PMR (benzene-d_6) for (-)-2: The aldehyde proton signal (δ 9.18) of (+)-1 had disappeared and two coupled doublets were found at δ 3.73 and 3.83 (1H each, J=13 Hz, CHHOH).

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9. Typical reaction mixture: 180 ml of 0.1 M phosphate buffer (pH 8.3) containing 260 μmol NAD^+, 3.3 mmol FMN, 1.7 ml Tween 80 and 170 mg (±)-5. 800 U, 400 U and 400 U of the enzyme were added at 0, 30, and 53 hr, respectively. The mixture was stirred at 30 °C for 69 hr.

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13. Each (-)-enantiomer moved faster than the antipode. Although the stereochemistry for (-)-5 and (-)-6 has not been reported, the common chromatographic behavior and the common enzymic unreactivity suggest that both levorotatory enantiomers have the same R configuration as (-)-4.[10]

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