Enantioselective Transfer Hydrogenation of Ketones using a Rhodium Catalyst containing a Methionine Sulphoxide Ligand

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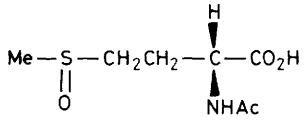
An *in situ* rhodium catalyst containing *N*-acetyl-(*S*)-methionine (*R,S*)-sulphoxide, and using propan-2-ol as a source of hydrogen, effects enantioselective hydrogenation of alkyl aryl ketones with up to 75% enantiomeric excess.

The most effective catalytic asymmetric hydrogenation of prochiral ketones to give optically active alcohols (with up to 82% enantiomeric excess, e.e.) has been accomplished using a rhodium catalyst containing chiral 2,4-bis(diphenylphosphino)pentane, at high H_2 pressure (70 atm); the synthesis of the phosphine ligand involves a lengthy, multistep procedure.[1] We report here on a catalytic rhodium hydrogen-transfer system (using propan-2-ol as the source of hydrogen) that effects a comparable asymmetric hydrogenation and, of key importance, the chiral ligand, a new type, is a simple derivative of the naturally occurring, cheap, and readily available amino acid, (*S*)-methionine.

The air-stable ligand used is *N*-acetyl-(*S*)-methionine (*R,S*)-sulphoxide (AMSO), and is made by a standard acetylation† of (*S*)-methionine (*R,S*)-sulphoxide, which is prepared according to a literature procedure involving H_2O_2 oxidation of commercially available (*S*)-methionine;[2] this oxidation is non-enantioselective at the sulphur and yields a racemic sulphoxide centre.[2,3]



AMSO

The *in situ* catalyst system requires a Rh^I precursor, and operates optimally with added AMSO and KOH (Rh : AMSO : KOH = 1 : 2 : 4—5). The Rh (*ca.* 2.5×10^{-3} M) was dissolved with the AMSO and added ketone substrate (*ca.* 1.0 M) in propan-2-ol (10 ml), and the mixture refluxed for a few minutes under Ar; the base was then added,‡ and the refluxing continued for the desired reaction time (Table 1); the amounts of acetone detected show that propan-2-ol is the source of hydrogen. Without added hydroxide or alkoxide, there was no hydrogenation of the ketone; addition of the commonly used cocatalyst base NEt_3[7] again gave no conversion. Dialkyl ketones were not effectively hydrogenated under conditions that were optimum for the alkyl aryl ketones, an observation made by others using Rh–phosphine systems.[7] Of

† Methionine sulphoxide was stirred with acetic anhydride (1 : 1) in glacial acetic acid for 6 h at 10 °C; evacuation to dryness and repeated crystallisations from absolute ethanol yielded the white solid AMSO in 70% yield. The compound {$[\alpha]_D^{20}$ +26° (H_2O, *c* 5)} was fully characterized by elemental analysis; i.r.: ν(SO) 1025 cm^{-1}; ^1H n.m.r.: δ (25 °C, $CDCl_3$) 9.0 (br, NH), 8.01 (s, CO_2H), 4.43 (m, CH), 2.68 [m, S(O)–CH_2], 2.48 [s, $CH_3S(O)$], 2.05 (m, CH_2-CH), and 1.85 [s, C(O)–CH_3].

‡ The ketone substrate must be added first, otherwise Rh metal precipitates, and there is no effective hydrogenation; others have commented on a required order of addition of reagents in similar base- and Rh-catalysed hydrogen transfer reactions.[6] Metal formation is also observed when KOH : Rh < 3 : 1.

Table 1. Enantioselective hydrogenation of ketones using rhodium–AMSO transfer hydrogenation catalysts.[a]

	% Conversion	% Optical yield[b]
PhCOMe	22	38
	33[c]	41
	45[d]	63
	8[e]	1.2
	48[f]	22
	40[g]	37
p-MeC_6H_4COMe	31[d]	75
PhCOEt	21[d]	71

[a] Reaction time 8—10 h, using $[RhCl(hd)]_2$ as precursor; base (usually KOH) : AMSO : Rh = 5 : 1 : 1, unless stated otherwise. [b] The enantiomer obtained in excess from PhCOMe was always (*R*)-1-phenylethanol; optical yield estimated after work-up (distillation) by polarimetry {$[\alpha]_D^{22}$ of (*R*-PhCH(OH)Me +52.5°, *c* 2.27 in CH_2Cl_2[4]}, and confirmed using the chiral shift reagent tris[(+)-dicampholylmethanato]europium(III) by monitoring the α-hydrogen atom. The same shift reagent was used to estimate the e.e. of the product from *p*-MeC_6H_4COMe; an observed (+) rotation almost certainly refers to the (*R*)-alcohol. The enantiomer obtained in excess from PhCOEt was (*R*)-PhCH(OH)Et, as measured by polarimetry {$[\alpha]_D^{22}$ of neat (*S*)-enantiomer −28.1°}.[5] [c] KOH : Rh = 4.0 : 1. [d] AMSO : Rh = 2.0 : 1. [e] KOH added as aqueous solution (2 ml). [f] NaOMe added as base. [g] KOBu^t added as base.

a range of Rh^I precursors that were tested, $[RhCl(hd)]_2$§ gave somewhat higher optical yields than $[RhCl(cod)]_2$ while systems based on $[RhCl(nbd)]_2$ and $[RhCl(coe)_2]_2$ gave e.e. values of ≤10%. Use of iridium(I) precursors such as $[IrCl(cod)]_2$ and $[IrCl(coe)_2]_2$ under comparable conditions gave marginally higher conversions of acetophenone into the alcohol but the enantiomeric excesses were negligible.

The *in situ* Rh^I systems are clearly quite effective for the alkyl aryl ketone substrates and circumvent the use of high hydrogen pressure which is necessary in the chiral phosphine systems, although these give a somewhat higher e.e.[1] Systems that use corresponding Rh^I and Ir^I precursors, in the presence of a readily synthesized chiral Schiff base [*e.g.* from pyridine-2-carbaldehyde and (*R*)- or (*S*)-1-phenylethylamine], catalyse similar H_2-transfer from basic propan-2-ol solutions, but maximum optical yields were only 23% for acetophenone, and 33% for propiophenone;[8] isolated species containing the Schiff base (N—N) chelated *via* pyridine- and imine-nitrogen atoms, *e.g.* $[Ir(cod)(N—N)]^+ClO_4^-$, could also be used as catalysts.[8] We have been unable to isolate any pure Rh^I AMSO compounds, but the chelating ability, through sulphoxide and carboxylate, of this new bifunctional ligand is almost certainly utilized in the catalysis. On the basis of work which describes formation of $[RhCl(coe)(R_2SO)]_2$ complexes (R = $[CH_2]_2$ or Ph) that contain *S*-bonded sulphoxide,[9] co-ordinated diene within the Rh^I precursors is unlikely to be displaced by AMSO, and the variation in activity with choice of precursor is consistent with this. Of note, use of methionine sulphoxide itself as ligand does not generate effective catalysts; the acylation probably prevents binding *via* the amine-N, thereby promoting interaction with the sulphoxide moiety. The high enantioselectivities observed, and the fact that *in situ* Rh^I–R_2SO species are ineffective for catalytic H_2-transfer,[9,10] indicate that the carboxylate is co-ordinated also, at least during a key hydride transfer step.[6—8,11] Amino acid complexes of the type $[Rh(cod)\{NH_2CH(R)CO_2\}]$, and the acylated, bridged carboxylate derivatives $[Rh_2(cod)_2\{\mu\text{-}O_2CCH(R)NHCOMe\}_2]$ are poor hydrogenation catalysts generally;[12,13] even in the presence of tertiary phosphines, that stabilize Rh^I against reduction to metal, the acyl species give a maximum of 7% e.e. (for hydrogenation of prochiral unsaturated acids).[13]

The role of added base, a commonly used cocatalyst in ketone hydrogenation (using H_2 or propan-2-ol), is poorly understood generally; removal of Cl^-, or its replacement by OH^- or OR^- within the co-ordination sphere, including generation of polynuclear species with bridging alkoxides, are all possibilities.[7] A plausible key intermediate, consistent with the admittedly qualitative observations, would be $[Rh(hd)(AMSO)(ketone)]^+$; the usually postulated steps for the catalytic process (*e.g.* propoxide co-ordination, hydride abstraction, and transfer to substrate[6—8]) could be accommodated by changes in ligand denticity.

Although the chemistry of our system is poorly defined as yet, we feel that the ambidentate nature of the sulphoxide group, and the several bonding modes available for carboxylate, make a bifunctional ligand such as AMSO particularly attractive for applications in homogeneous catalysis, and the present work demonstrates the potential of such a ligand in asymmetric hydrogenation.

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§ hd = hexa-1,5-diene, cod = cyclo-octa-1,5-diene, nbd = norbornadiene, coe = cyclo-octene.

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