Rhodium(I)–Sulfonated-bdpp† Catalysed Asymmetric Hydrogenation of Imines in Aqueous–Organic Two-phase Solvent Systems

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The imines ArC(Me)=NCH$_2$Ph (Ar = Ph, 2-MeO-C$_6$H$_4$, 3-MeO-C$_6$H$_4$, 4-MeO-C$_6$H$_4$) are hydrogenated to the corresponding amines with extremely high enantioselectivities up to 96% under very mild conditions, using rhodium complexes associated with sulfonated bdpp.

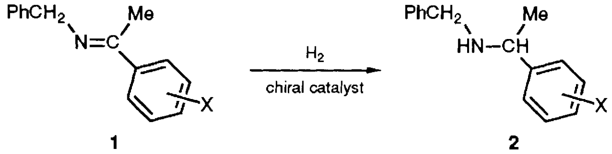
Catalytic asymmetric hydrogenation of prochiral alkenes[1] and ketones[2] has been extensively investigated and various homogeneous catalysts have been found to be efficient in the asymmetric hydrogenation of imines.[3–5]

In this paper we present the first example of asymmetric catalytic hydrogenation of imines in a two-phase system using a water-soluble catalyst to give secondary amines with almost complete enantioselectivity [>90% enantiomeric excess (e.e.)].[6]

The catalytic hydrogenation of imines **1–3** was carried out as follows. The cyclooctadiene (cod) dimer [Rh(cod)Cl]$_2$ (0.025 mmol) and an appropriate amount of sulfonated-bdpp[7] were dissolved in 10 ml of degassed H$_2$O–AcOEt (1 : 1) in a Schlenk tube, under an argon atmosphere. The substrate (5 mmol) was then added. The two-phase liquid mixture was transferred to a 20 ml stainless steel autoclave under argon, degassed three times with H$_2$ (70 bar) then pressurised to 70 bar, and the contents stirred for 6 h at 20 °C. The amines were recovered in almost quantitative yield from the reaction mixture by separation of the organic phase followed by pumping off the solvent and distillation of the residue under vacuum.

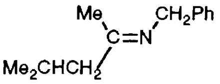
The hydrogenation is quite chemoselective, although a small amount of primary amine and ketone generated by hydrolysis of the imine are observed.

The data in Table 1 show that the *in situ* catalyst is most effective for hydrogenation of **1a–d** when the degree of sulfonation of the phosphine is below 2, and when the reaction is performed in H$_2$O–AcOEt two-phase solvent system. This unprecedented high enantioselectivity (96%) and mild reaction condition appears to be superior to that known for hydrogenation of the C=N double bond of imines. Kang *et al.*[4]



1 **2**

a; X = H **b**; X = 4-OMe **c**; X = 3-OMe **d**; X = 2-OMe



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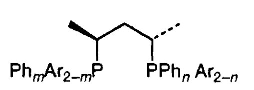

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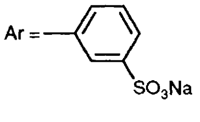

a; m = 2, n = 2
b; m = 1, n = 2
c; m = 1, n = 1
d; m = 0, n = 1
e; m = 0, n = 0

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† bdpp = (−)-(2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane.

Table 1 The asymmetric hydrogenation of imines[a]

Substrate	Sulfonation degree of the ligand[b]	Solvent	Yield of amine (%)	E.e. (%)[g]
1a	3.75[c]	H_2O-AcOEt	55	19
1a	2.21[d]	H_2O-AcOEt	41	32
1a	1.65[e]	H_2O-AcOEt	94	96 (95)
1a	1.41[f]	H_2O-AcOEt	96	96 (88)
1a	1.41[f]	H_2O-C_6H_6	67	75
1a	1.41[f]	H_2O-MeC_6H_5	34	55
1a	1.41[f]	H_2O-CH_2Cl_2	84	7
1a	0	H_2O-AcOEt	87	18
1a	0	MeOH	96	84
1a	0	H_2O-MeOH	11	30
1b	1.65[e]	H_2O-AcOEt	96	95 (86)
1c	1.65[e]	H_2O-AcOEt	93	89 (86)
1d	1.65[e]	H_2O-AcOEt	94	91 (92)
3	2,21[d]	H_2O-AcOEt	92	0

[a] *Conditions*: [Rh^I] : [sulfonated bdpp] : [substrate] = 1 : 1.1 : 100, at 20 °C, reaction time is 6 h. [b] Composition of the ligand used was determined by HPLC.[7] [c] 25% **4d** and 75% **4e**. [d] 79% **4c** and 21% **4d**. [e] 35% **4b** and 65% **4c**. [f] 59% **4b** and 41% **4c**. [g] The e.e. of the amines was determined by two methods: (*i*) ^1H NMR (300 MHz) spectroscopy: optically pure mandelic acid as a chiral solvating agent induced nonequivalence ($\Delta\delta = 0.25$ ppm) in the signals of methyl and methine protons of the amines; (*ii*) HPLC of the Mosher derivatives (values in parenthesis) using Spherisorb S50D2 as the column (150 × 4.6 mm), and MeCN : H_2O (60 : 40) as the eluent. Details of these methods will be described in the future. Product configuration is (*R*) in all cases.

have reported 91% e.e. for the hydrogenation of **1a** using an *in situ* Rh^I-(*R*)-1,2-bis(diphenylphosphino)-1-cyclohexylethane system in the presence of iodide cocatalyst, but the reduction was carried out at −25 °C and took 144 h.

Although the number of water-soluble organometallic catalysts[7–12] is steadily growing, to our knowledge, this is the first example of a systematic comparison of the performance of a chiral ligand containing various numbers of sulfonate groups. Compounds **4b–e** have not been separated, however, determination of the ligand composition has been made by HPLC.[7] Thus, the degree of sulfonation could be calculated. The extent of asymmetric induction as a function of degree of sulfonation or composition of the ligand shows that the presence of monosulfonated derivative **4b** is important for high chiral discrimination, in spite of that, this is a mixture of two diastereoisomers. Thus, the present reaction not only introduces a novel class of enantioselective reduction of C=N double bonds using a water-soluble transition metal complex as catalyst, but suggests that this approach to the synthesis of new catalysts has great promise.

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