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IMPROVING ENANTIOSELECTIVITY BY USING A MONO-SULPHONATED DIPHOSPHINE AS LIGAND FOR HOMOGENEOUS IMINE HYDROGENATION

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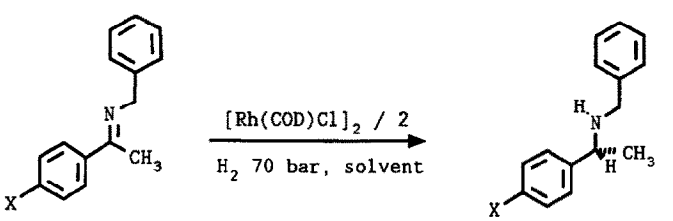
Abstract: The Rhodium catalysed hydrogenation of acetophenone N-benzylimine using mono-sulphonated (2S,4S)-bis-(diphenylphosphino)pentane as ligand gives the corresponding amine with 94% e.e., whereas use of the di-sulphonated ligand yields product with 2% e.e.

The homogeneous asymmetric hydrogenation of prochiral imines to yield chiral secondary amines is an emerging area of asymmetric homogeneous catalysis.[1] Low to medium enantiomeric excesses are usually obtained. However, a new development emerged when Bakos and Sinou working on water-soluble catalysts used partially sulphonated (2S,4S)-bis-(diphenylphosphino)pentane (2S,4S-BDPP, **2a**) as ligand for the rhodium catalysed hydrogenation of acetophenone N-benzylimine (**1**) in a two phase system (H_2O/EtOAc).[2] They found that the optical yields obtained depended strongly on the sulphonation degree of the diphosphine ligand.



1 3

Scheme 1

In fact almost complete enantioselectivity was observed when the degree of sulphonation was kept between 1.2 and 1.7, whereas with the tetra-sulphonated ligand **2e** the amine **3** was obtained with an e.e. of 58%[3]. The sulphonation of **2a** yields a mixture of mono- (**2b**), di- (**2c**), tri- (**2d**) and tetra- (**2e**) sulphonated 2S,4S-BDPP, complicated by the presence of epimers because of the chirality on phosphorus that is introduced with sulphonation.[4] These seemingly contradictory facts are best reconciled by assuming the presence of a single highly enantioselective and kinetically superior catalyst in the resulting mixture of rhodium complexes. This

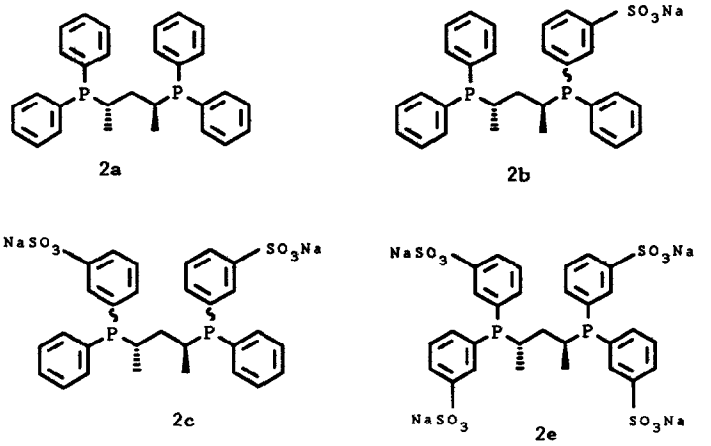


Figure 1. Diphosphine ligands

paper describes the isolation and characterisation of this component.

The sulphonation of **2a** was conveniently monitored using RP-HPLC and was carried on to give a mixture consisting mainly of **2b** and **2c** (Figure 2a). Compounds **2b** and **2c** were separated by column chromatography on a Silica-60 column.[5] The epimeric phosphines however, could not be separated. The analogous bis-phosphine oxides **3b** and **3c** were obtained upon oxidation of **2b** and **2c** with H_2O_2. They were readily separated by HPLC and are present in statistical amounts (Figure 2b). The ^{31}P nmr spectra of **2b**, **2c**, **3b** and **3c** are in agreement with the proposed structures.[5]

Compounds **2b** and **2c** form complexes when reacted in a 2:1 ratio with $[Rh(COD)Cl]_2$ in CH_3OH or CH_2Cl_2/H_2O. ^{31}P nmr spectroscopic data of these complexes are characteristic of cationic complexes.[6,7] The mono-sulphonated ligand **2b**, for example, consisted of equal amounts of two epimers

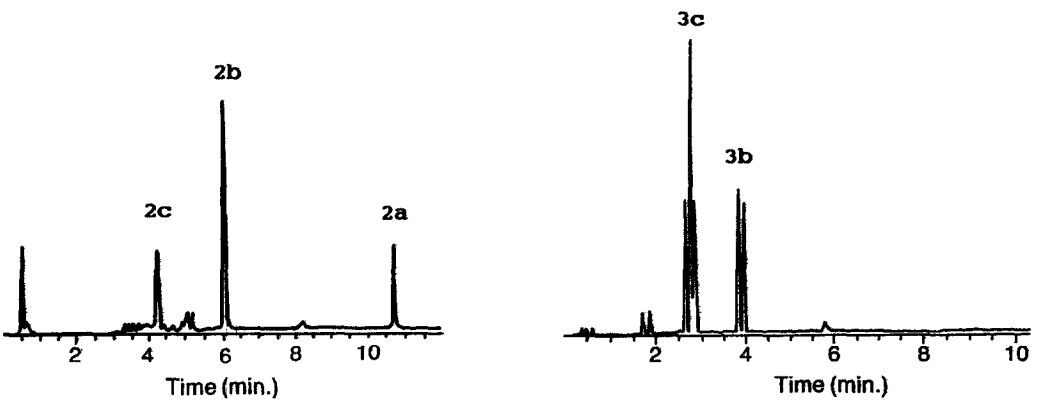


Figure 2. HPLC trace of sulphonation mixture (**a**). Same mixture after treatment with H_2O_2 (**b**)

and it yielded two different complexes with $[Rh(COD)Cl]_2$. Each complex gives rise to a doublet of doublets for each phosphorus atom resulting in a sixteen line spectrum. The di-sulphonated ligand **2c** yielded three different complexes with $[Rh(COD)Cl]_2$. An FAB-MS spectrum of the complex formed from **2b** and $[Rh(COD)Cl]_2$ displays a MH^+ peak at 731. This strongly suggests a structure for the complex Rh(COD)**2b** in which the SO_3^- of the ligand acts as the counterion for rhodium. This also confirmed by the fact that the complex from **2b** is only soluble in the organic phase, whereas the complex from **2c** only dissolves in the aqueous phase.

The catalysts for the hydrogenations of **1a-c** (Scheme 1) were prepared in situ from $[Rh(COD)Cl]_2$ and two equivalents of diphosphine ligand in a two-phase solvent mixture of H_2O(pH 12) and ethyl acetate. Hydrogenations were carried out in an autoclave at 20°C and 70 bar H_2. The imines **1a-c** were prepared from the corresponding ketones and benzylamine by azeotropic water removal from toluene[8]. Results are presented in Table 1.

Table 1. Hydrogenation of **1**[a]

Imine	X	Ligand	Solvent	Conversion after 1h (%)[b]	e.e. (%)[c]
1a	H	2a	CH_3OH	31	65
1a	H	2a	$EtOAc/H_2O$	no reaction	-
1a	H	2b	$EtOAc/H_2O$	85	94
1a	H	2b	EtOAc	not determined	94
1a	H	2c	$EtOAc/H_2O$	24	2
1a	H	2e	$EtOAc/H_2O$	not determined	58[3]
1b	OMe	2b	$EtOAc/H_2O$	not determined	92
1c	Cl	2b	$EtOAc/H_2O$	not determined	92

a. Rhodium:imine = 1:100, [imine] = 0.25 M, p = 70 bar

b. In all cases >98% conversion was reached. The product was isolated in >99% purity by Kugelrohr distillation.

c. Enantiomeric excess was determined by ^1H NMR using 2,2,2-trifluoro-1-(9-anthryl)ethanol as shift reagent. All products had R-configuration.

The hydrogenation of **1a** (X = H) with **2b** as catalyst ligand yielded the corresponding amine R-**3a** with an e.e. of 94 %. Using **2c** as the catalyst ligand, hydrogenation of **1a** proceeded with only 2 % e.e. Hydrogenation of **1b** (X = OMe) and **1c** (X = Cl) gave the corresponding amines also with an high e.e. of both 92 %.[9]

Comparison of reaction rates confirmed the kinetic superiority of the mono-sulphonated catalyst which we found to be about five times faster in the hydrogenation of **1a** than the catalysts based upon BDPP(**2a**) or the di-sulphonated analog (**2c**). We are currently investigating the scope of this mono-sulphonation concept with regard to other substrates and ligands.

References

1. (a) Levi, A.; Modena, G.; Scorrano, G. *J. Chem. Soc. Chem. Commun.*, **1975**, 6. (b) Vastag, S.; Bakos, J.; Toros, S.; Tahoch, N.E.; King, R.B.; Heil, B.; Marko, L. *J. Mol. Catal.*, **1984**, 22, 283. (c) Kagan, H.B.; Langlois, N.; Dang, F.P. *J. Organomet. Chem.*, **1975**, 90, 353. (d) Kang, G.J.; Cullen, W.R.; Fryzuk, M.B.; James, B.R.; Kutney, J.P. *J. Chem. Soc. Chem. Commun.*, **1988**, 1466. (e) Bakos, J.; Toth, I.; Heil, B.; Marko, L. *J. Organomet. Chem.*, **1985**, 279, 23. (f) Bakos, J.; Toth, I.; Heil, B.; Szalontai, C.; Parkanyi, L.; Fulop, V. *J. Organomet. Chem.*, **1989**, 370, 263. (g) Cullen, W.R.; Fryzuk, M.D.; James, B.R.; Kutney, J.P.; Kang, G.-J.; Herb, G.; Thornburn, I.S.; Spogliarich, R. *J. Mol. Catal.*, **1990**, 62, 243. (h) Cheong Chan Y.Ng.; Osborn, J.A. *J. Am. Chem. Soc.*, **1990**, 112, 9400.
2. Bakos, J.; Heil, B.; Lecomte, L.; Sinou, D. Fifth IUPAC Symposium on Organometallic Chemistry directed towards Organic Synthesis, Poster 46, 1989, Florence (Italy).
3. Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics*, **1989**, 8, 542.
4. While this work was in progress a paper describing the HPLC analysis of the sulphonation products of several chiral diphosphines appeared in the literature! Lecomte L.; Sinou, D. *Phosphorus, Sulfur and Silicon*, **1990**, 53, 239.
5. The sulphonation of **2a** was carried out using the following conditions. **2a** (5.0g, 11.4 mmol) was dissolved in 5 mL conc. H_2SO_4 and cooled at 10 ^oC. 30% SO_3 in H_2SO_4 (50 mL) was added dropwise. After 1h 15 min the reaction was quenched by pouring the reaction mixture on to 200g ice. Neutralisation with 50% NaOH followed by precipitation of the Na_2SO_4 with methanol yielded a crude product which consisted mainly of **2b** and **2c**. Compounds **2b** and **2c** were separated by column chromatography on a Silica-60 column. Elution with ethyl acetate/methanol/water/acetic acid (80:10:5:5) yielded 2.62g **2b** as an equal mixture of two epimers. Subsequent elution with ethyl acetate/methanol/water/acetic acid (50:30:10:10) yielded 3.32g **2c** as a mixture of three epimers in a 1:2:1 ratio. Satisfactory elemental analyses were not obtained due to persistent contamination with Na_2SO_4. HPLC was carried out on a C18 reverse-phase column(10cm, 3mm), flow rate 1mL/min, eluent gradient phosphate buffer pH 7.5/CH_3CN (5-100% in 10 min). ^{31}P (in CD_3OD): **2b** 0.90(2P), 0.69 and 0.27 ppm; **2c** 0.89, 0.64, 0.42 and 0.24 ppm; **3b** 42.0(2P), 43.0 and 43.58 ppm; **3c** 41.2(2P), 41.35(d, 2.2Hz) and 41.13(d, 2.2Hz). FAB-MS: calcd. for $C_{29}H_{31}O_5P_2S$ (**3b**) M = 552, found MH^+ = 553, MNa^+ = 575, MK^+ = 591; calcd. for $C_{29}H_{30}O_8P_2S_2P$ (**3c**) M = 632, found MNa^+ = 655, MNa_2^+ = 677.
6. $[Rh(COD)Cl]_2$ + **2b**: 30.06 (P_A, J_{Rh-P} = 144.0, J_{P-P} = 46.3), 27.98 (P_B, J_{Rh-P} = 142.1, J_{P-P} = 46.3); 28.60 (P_A', J_{Rh-P} = 143.0, J_{P-P} = 46.5), 28.12 (P_B', J_{Rh-P} = 141.8, J_{P-P} = 46.5). $[Rh(COD)Cl]_2$ + **2c**: 29.94 (J_{Rh-P} = 143.9); 28.94 (J_{Rh-P} = 142.1); 29.65(P_A, J_{Rh-P} = 142.8, J_{P-P} = 47.0), 29.13 (P_B, J_{Rh-P} = 143.2, J_{P-P} = 47.0)
7. See e.g. Slack, D.A.; Greveling, I.; Baird, M.C. *Inorg. Chem.*, **1979**, 18, 3125.
8. Texier-Boullet, F. *Synthesis*, **1985**, 6, 679.
9. Imines **1b** and **1c** and amines **3b** and **3c** were characterised by ^1H NMR, ^{13}C NMR and absolute mass determination.