Influence of degree of sulfonation of BDPP upon enantioselectivity in rhodium–BDPP catalyzed hydrogenation reactions in a two phase system

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Abstract

Asymmetric hydrogenation experiments were carried out with catalysts prepared in situ from [Rh(COD)Cl]$_2$ and 2 eq. of a sulfonated (2S,4S)-bis-2,4-(diphenylphosphino)pentane carrying 0–4 sulfonate groups, in a two phase aqueous organic system. The effect of degree of sulfonation on enantioselectivity was determined in the hydrogenation of one imine and three olefin substrates. In the hydrogenation of the substrates N-benzylacetophenoneimine (**2**) and dimethyl itaconate (**8**) the monosulfonated ligand **1b** was by far superior; hydrogenation using this ligand proceeded with 94% and 28% ee, respectively, whereas use of bis- or trissulfonated ligand gave practically racemic product. In the hydrogenation of N-acetamidocinnamic acid (**4**) or methyl ester (**6**) enantioselectivity decreased with degree of sulfonation. The mono sulfonation effect is not due to steric or electronic reasons, nor is an anion effect involved.

1. Introduction

Homogeneous asymmetric hydrogenation is slowly emerging as a useful tool in the production of enantiopure fine chemicals. Yet the number of industrial processes using asymmetric homogeneous hydrogenation are few compared to the enormous effort in academic research [1]. The lack of a good method for separation of catalyst from product is one of the reasons why this technique is often less economical than classical resolution of diastereomeric salts or use of enzymes. The metal can be recovered in some form by relatively simple means but the ligand is usually lost. Because of the expense of the ligand only reactions with extremely high turnover numbers have been commercialized. Obviously, a device allowing a simple recycle of catalyst commensurate with use in multi-purpose reactors would greatly enhance the scope of homogeneous asymmetric hydrogenation in industrial applications. Following this analysis, several groups have become interested in developing water soluble catalysts for use in two phase systems. This methodology allows the easy recycling of

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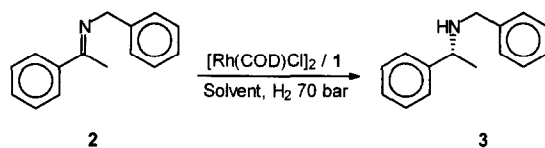
Scheme 1. Asymmetric hydrogenation of 2 using [Rh(COD)Cl]$_2$/1 as catalyst.

the catalyst by reuse of the aqueous phase after separating the product which remains exclusively in the organic phase [2–4].

We became interested in water soluble catalysts when working in the area of asymmetric imine hydrogenation. The rhodium–diphosphine catalyzed hydrogenation of a selected number of imines proceeds with medium to high enantioselectivity, but in all reported instances the reaction is slow, with turnover frequencies in the order of 1–10 h^{-1} [5]. Amrani et al. did pioneering work in this area by establishing that use of the tetrasulfonated diphosphine ligand (2S,4S)-2,4-bis(diphenylphosphino)pentane (BDPP) (1e) in the rhodium catalyzed hydrogenation of imines in an aqueous/organic two phase system gave rise to only slightly reduced enantioselectivities when compared to the parent diphosphine 1a and allows for easy recycling of the catalyst [6]. However, the enantioselectivity of this reaction is still not high enough for practical use.

An interesting new development emerged when Bakos et al. found that the use of BDPP ligand that was only partially sulfonated (i.e., less than 4 sulfonate groups) gave rise to very high enantioselectivities in the two phase rhodium catalyzed hydrogenation of N-benzylacetophenoneimine (2) (Scheme 1) [7]. This extraordinary effect is hard to explain in view of the fact that an incompletely sulfonated bisphosphine consists of a mixture of phosphines which differ in degree of sulfonation. In addition, the sulfonation of only one of the aryl groups attached to a single phosphorus atom as in 1c and 1d creates chirality at phosphorus resulting in the formation of epimers (Scheme 2).

Working on the assumption that one of the ligands in this mixture forms a complex with rhodium that is highly enantioselective and kinetically superior, we proceeded to isolate the monosulfonated and the disulfonated ligand [8]. This was accomplished by chromatography over silica. Diastereomers due to chirality on phosphorus where inseparable, even on analytical HPLC. However, oxidation of the phosphines with H$_2$O$_2$ gave the bisphosphine oxides, that could be separated on analytical HPLC (Fig. 1).

From this, it became clear that sulfonation proceeds with zero induction. A statistical distribution of the diastereomers was found: a 1:1 mixture of the mono-sulfonated ligand and a 1:2:1 mixture of the bissulfonated ligand.

Catalysts were prepared in situ from [Rh(COD)Cl]$_2$ and 2 equivalents of ligand. Hydrogenation of N-benzylacetophenoneimine was performed with these in situ prepared catalysts at a pressure of 70
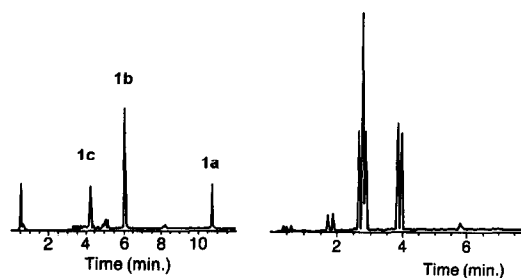
Fig. 1. HPLC trace of sulfonation reaction of 1a (75 min) before and after treatment with H$_2$O$_2$ (right).
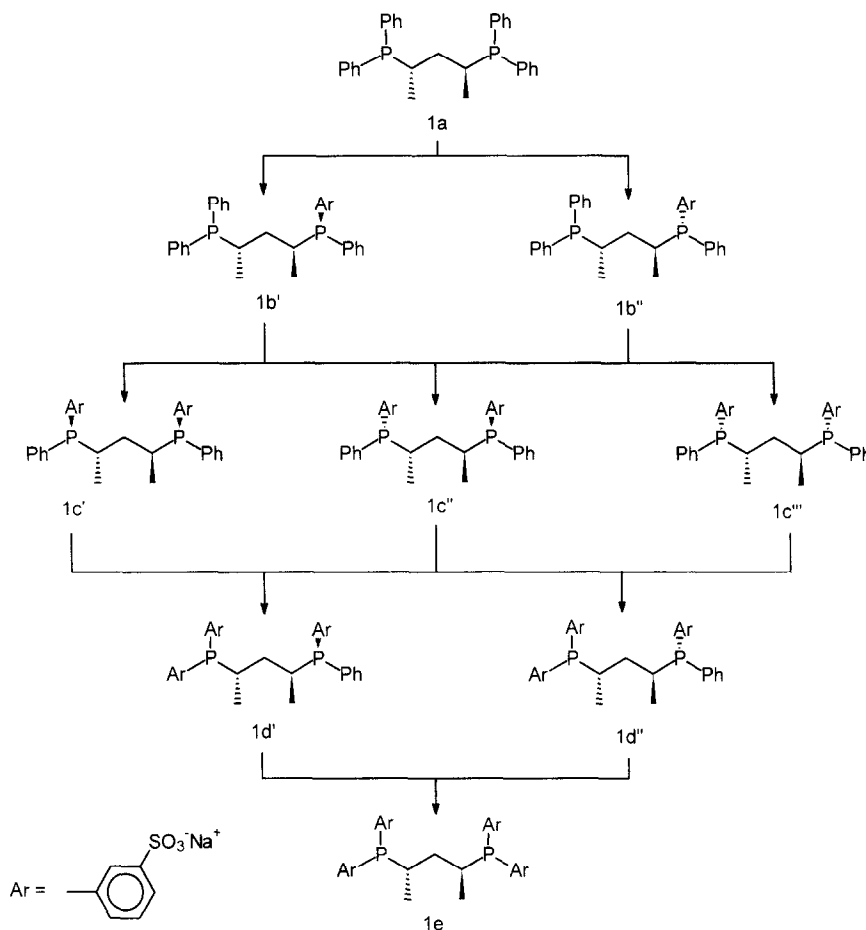
Scheme 2. Products of the sulfonation of **1a**.

bar H_2 in a two phase system (EtOAc/H_2O). These experiments revealed that the rhodium-complex with monosulfonated ligand gave the amine product in 94% ee, whereas with the bissulfonated ligand a practically racemic product was obtained [8].

From the coloration of the two phases it became clear that the catalyst formed from **1b** dissolves in the organic phase only, which can be explained by the formation of an internal ion pair (Fig. 2). The complex with **1c** dissolves exclusively in the aqueous phase.

In view of the fact that the monosulfonated ligand is a 1:1 mixture of diastereomers, it is hard to find an explanation for the high enantioselectivity based upon steric grounds. A number of other hypotheses can be advanced that can be verified by experimental means. One hypothesis is based on
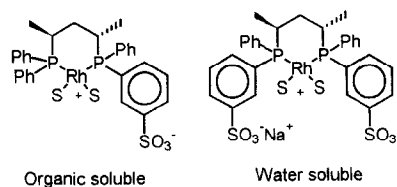

Organic soluble   Water soluble

Fig. 2. Relation between solubility of rhodium complexes and degree of sulfonation.

the assumption that difference in electron density at the two phosphorus atoms is the key factor. If this is the case, one would expect to find a reasonably high enantioselectivity in these hydrogenation reactions if the trissulfonated ligand is used. For this reason we decided to synthesize and isolate trissulfonated BDPP (**1d**). Preparation of the ligands with all other possible degrees of sulfonation had been described before [6,8].

It is also possible that the peculiar monosulfonation effect is due to some interaction that is related to the imine substrate. Exploration of the hydrogenation of other prochiral substrates could shed additional light on this matter.

Another verifiable hypothesis rests on the assumption that the high enantioselectivity is a consequence of the formation of a cationic complex which has an internal sulfonate as anion. Using other cationic rhodium(BDPP) complexes as catalyst should therefore lead to higher enantioselectivity than the analogous chloride.

This paper describes the results of these experiments aimed at understanding the origin of the high enantioselectivity with the monosulfonated rhodium complex in the imine hydrogenation.

2. Experimental

2.1. Materials and methods

GC analyses were performed on a HP 5890 Series II gas chromatography apparatus using a capillary Chrompack CP Sil 5CB column (25 m × 0.32 mm). For analyses of amines a carbowax column was used. HPLC analyses were performed using a Nucleosil 120-5 C18 rp column (25 × 0.46 cm); 2 ml/min; Solvent A: phosphate buffer pH 5; Solvent B: CH_3CN; gradient: 3 min 1% B, 1–50% B in 17 min. Hydrogenations were performed in a 50 ml Parr autoclave made from Hastelloy C at 70 bar H_2. Solvents were dried and freed from oxygen by distillation from the appropriate drying agents under an atmosphere of argon. Other solutions that were used in the preparation of phosphines or in hydrogenation reactions were freed of oxygen by bubbling argon or nitrogen through it. Imine substrates were prepared according to a literature prescription [9] and purified by crystallization from hexane. Methyl-Z-α-acetamidocinnamate, Z-α-acetamidocinnamic acid, dimethyl itaconate, (2S,4S)-2,4-bis(diphenylphosphino)pentane (BDPP), [Rh(COD)Cl]$_2$ and Rh(CO)$_2$Acac were obtained commercially, and used without further purification. Sulfonation of (2S,4S)-2,4-bis(diphenylphosphino)pentane to mainly **1b** and **1c**, and their purification was described before [8]. Preparation of **1e** has been described in the literature [6]. All reactions with and handling of phosphines was performed under argon.

2.2. Preparation of 1d

BDPP (1.06 g, 2.4 mmol) was dissolved in concentrated H_2SO_4 (2 ml) and the solution was cooled to 0°C. Oleum (30% SO_3 in concentrated H_2SO_4) was slowly added in such a way that the temperature remained below 5°C. The solution was allowed to come to room temperature and after 68 h the reaction was stopped by adding the mixture to 200 ml of ice cold water. The resulting solution was carefully neutralized with 50% NaOH to pH 7, while keeping the temperature below 30°C. Na_2SO_4 was precipitated by the addition of 150 ml of methanol. After filtration the filtrate was concentrated to dryness and the residue treated again with 100 ml of methanol. The mixture was filtered and the solvent was removed from the filtrate by evaporation to give a white powder (1.7 g)

which consists of a mixture of **1c**, **1d** and **1e**. Column chromatography over silica-60 eluting with a mixture of EtOAc/MeOH/HOAc/H_2O (60:30:5:5) and pooling of pure fractions gave **1d**. To ensure that **1d** is entirely in the sodium form, the powder was dissolved in 20 ml of water and 1 M NaOH was added to pH 8. The solution was filtered over a plug of silica and evaporated to give a white powder (1.16 g, 1.55 mmol). ^{31}P-NMR (H_2O): Diastereomer A: δ 1.18 and 0.76; Diastereomer B: δ 0.76 and 0.56. For further characterization **1d** was oxidized with excess of 30% H_2O_2 to the bisphosphineoxide. HPLC: Two peaks in 1:1 ratio at 8.53 and 8.83 min. ^{31}P-NMR (H_2O): Diastereomer A: δ 44.42 and 43.61; Diastereomer B: δ 44.21 and 43.49.

2.3. Rh(COD)(1d)Cl

[Rh(COD)Cl]$_2$ (20.2 mg, 0.049 mmol) and **1d** (59.2 mg, 0.0793 mmol) were dissolved in 1.0 ml CD_3OD in a 10 mm NMR tube. The ^{31}P-NMR:

Complex	δ P_A (ppm)	δ P_B (ppm)	[1]J(Rh, P_A) (Hz)	[1]J(Rh, P_b) (Hz)	[2]J(P_A, P_B) (Hz)
Diastereomer 1	30.69	28.54	144.9	142.91	47.02
Diastereomer 2	29.53	28.65	144.5	142.07	46.98

2.4. Hydrogenation experiments

To a 5 ml vial were added a magnetic stirring bar, [Rh(COD)Cl]$_2$ (5.0 mg, 0.01 mmol), and 2.1 mol eq. of the ligand. The vial was sealed with a serum cap and flushed with argon. After addition of H_2O (2.0 ml) by syringe the solution was stirred at ambient temperature during 1 h. A solution of substrate (200 mol eq.) in 2.0 ml of EtOAC was added by syringe. A 1 inch needle was stuck into the serum cap and the vial was transferred to the autoclave. In this way, it is possible to perform several hydrogenations in one run. Stirring was started. The autoclave was flushed three times with H_2 and brought to the desired pressure of 10 bar (substrate **4**, **6** and **8**) or 70 bar (substrate **2**). After 16 h of hydrogenation at ambient temperature, the vials were opened and the contents worked up. The organic and aqueous phases were separated. After drying over Na_2SO_4, the organic phase was subjected to rotary evaporation. The residue was analyzed by GC and ^{1}H-NMR to determine the conversion and selectivity. All experiments were performed in duplicate.

2.5. Determination of enantiomeric excess

Liquid products were purified by bulb to bulb distillation and solid products were purified by column chromatography. Enantiomeric excess was determined by measuring the optical rotation of the product and comparison with literature values. ee of N-benzyl-1-phenylethylamine was determined by ^{1}H-NMR using 2,2,2-trifluoro-1-(9-anthryl)ethanol as shift reagent.

3. Results

3.1. Sulfonation of BDPP

Sulfonation of BDPP was carried out with excess oleum under argon. The course of the reaction was followed by HPLC. This allowed us to stop the reaction at the time when the desired ligand is
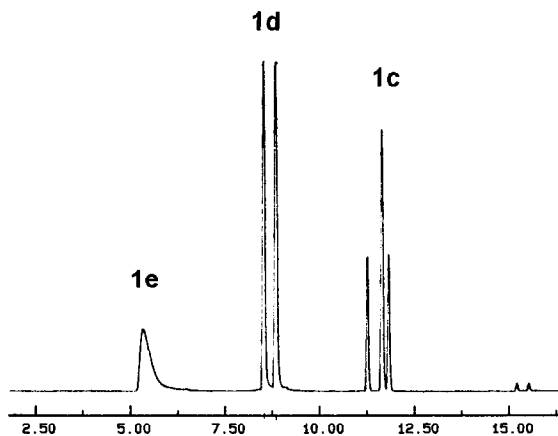
1d

Fig. 3. HPLC trace of sulfonation reaction of **1** (68 h) after treatment with H_2O_2.

present in optimal amounts. To obtain a mixture of predominantly **1b** and **1c**, the reaction was carried out at 0°C and was stopped after 1 h and 15 min. A mixture of mostly **1d** and **1e** was obtained after 68 h at room temperature. Both mixtures could be separated by column chromatography over silica. The isolated ligands are mixtures of diastereomers. The ratio of diastereomers could be determined by HPLC after oxidation with H_2O_2 to the corresponding bisphosphine oxides (Fig. 1 and Fig. 3).

3.2. Hydrogenation reactions

The effect of the degree of sulfonation on enantioselectivity was determined in the hydrogenation reactions on four structurally different substrates as depicted in Scheme 3.

In Table 1, we have summarized the results of these hydrogenation reactions. In all cases the hydrogenation reactions proceeded with high selectivity. No other products could be detected by GC or ¹H-NMR.
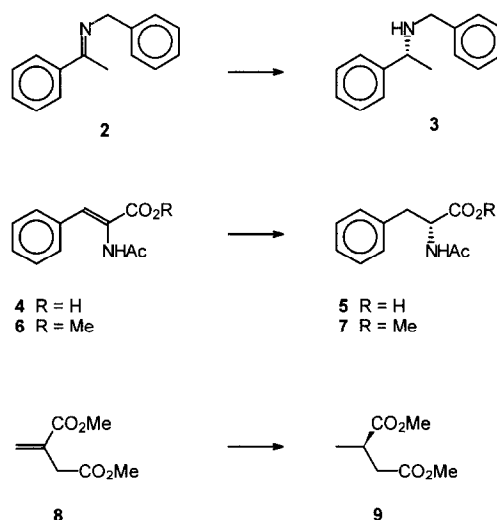
Scheme 3. Substrates and products of asymmetric hydrogenation reactions with [Rh(COD)Cl]₂ /**1**.

Table 1
Asymmetric hydrogenation reactions of substrates 2, 4, 6 and 8 with [Rh(COD)Cl]$_2$ and ligand 1a–e [a]

Substrate	Ligand	Solvent	Pressure (bar)	Conversion (%)	ee [b] (%)
2	1a	MeOH	70	100	68
	1a	EtOAc/H$_2$O	70	0	–
	1b	EtOAc/H$_2$O	70	100	94
	1c	EtOAc/H$_2$O	70	100	2
	1d	EtOAc/H$_2$O	70	99	3
	1e	EtOAc/H$_2$O	70	99	63
4	1a	MeOH	10	100	96
	1b	EtOAc/H$_2$O	10	100	87
	1c	EtOAc/H$_2$O	10	100	83
	1d	EtOAc/H$_2$O	10	100	75
	1e	EtOAc/H$_2$O	10	100	65
6	1a	MeOH	10	100	72
	1b	EtOAc/H$_2$O	10	100	74
	1c	EtOAc/H$_2$O	10	100	71
	1d	EtOAc/H$_2$O	10	100	59
	1e	EtOAc/H$_2$O	10	100	45
8	1a	MeOH	10	100	3
	1b	EtOAc/H$_2$O	10	100	28
	1c	EtOAc/H$_2$O	10	100	1
	1d	EtOAc/H$_2$O	10	100	1
	1e	EtOAc/H$_2$O	10	100	8

[a] Conditions: see experimental section.
[b] All products had the R-configuration.

The monosulfonation effect was observed only with imine 2 and to a lesser extent with dimethyl itaconate (8) as substrates. In the hydrogenation of N-acetamidocinnamic acid (4) and methyl ester (6) enantioselectivity decreased with increasing degree of sulfonation. This might be related to the fact that the latter two substrates complex to rhodium in a bidentate fashion, whereas imines are monodentate. From NMR experiments performed by Brown, it appears likely that dimethyl itaconate also forms a bidentate complex with cationic rhodium bisphosphine complexes [10]. However, the bond to the ester group must be weak and it is possible that under the aqueous conditions 8 is monodentate also.

These results also seem to indicate that different electron densities on phosphorus is not a key factor in the high enantioselectivity obtained with 1b because the use of 1e in the hydrogenation of imine 2 resulted in practically racemic product.

From the kinetic data in Fig. 4, it is clear that hydrogenation of 2 using 1b as ligand proceeds at a higher rate than with any of the other ligands. As the catalyst based on 1b is soluble in the organic phase this is presumably largely a kinetic effect related to the higher concentration of substrate in the organic phase.

We have attempted the hydrogenation of several other imine substrates using this procedure but a number of these did not react at all. As all reluctant substrates were oils rather than purified solids we decided to investigate whether some impurity in the imine acted as a poison. Hydrogenation of 2 with Rh–1b under the usual conditions proceeded normally in the presence of 5 eq. of acetophenone, but
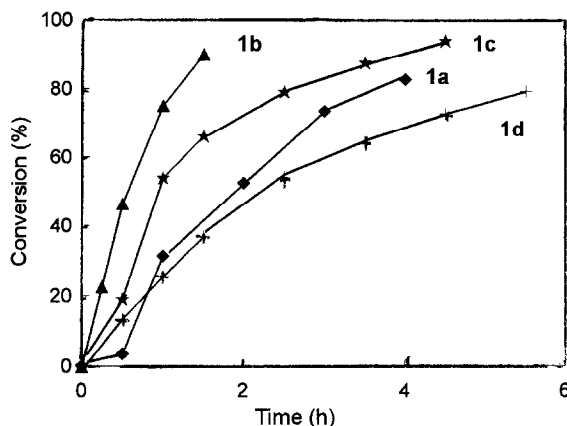
Fig. 4. Dependence of rate of hydrogenation of 2 upon degree of sulfonation of 1.

addition of 5 eq. of benzylamine lead to complete inhibition. The mechanism of this poisoning effect is unknown.

3.3. Anion effect

The catalyst based on **1b** is by necessity a cationic complex. Inspection of molecular models reveals that no direct interaction is possible between rhodium and the sulfonate anion. This leads to the suggestion that the high enantioselectivity using **1b** is solely due to an anion effect. It is even possible that cationic complexes in general will lead to higher enantioselectivity. However, Kang et al. found that halides and more in particular iodide have a positive effect on the enantioselectivity in the rhodium–cycphos catalyzed hydrogenation of imines [11]. Rhodium(BDPP) complexes containing a number of different anions were screened in the hydrogenation of **2** in methanol (Table 2).

With acetylacetonate as anion the reaction rate was retarded and low enantioselectivity was found. This can be explained by the fact that Acac is a bidentate ligand. Addition of KI also resulted in lower ee's. Iodide complexes are not cationic and the actual catalyst could be dimeric. It is not clear if the addition of the sodium salts of camphorsulfonic acid or benzoic acid leads to formation of the respective rhodium sulfonate and benzoate complexes as no NaCl precipitated. However, a bona fide cationic complex like the BF_4^--complex also gave the same ee as the chloride complex, although the

Table 2
Anion effect in the $[Rh(COD)Cl]_2$ /**1a** catalyzed hydrogenation of **2** [a]

Entry	Catalyst precursor	Added anion	Time (h)	Yield (%)	ee [b] (%)
1	$[Rh(COD)Cl]_2$	–	16	100	68
2	$[Rh(COD)Cl]_2$	Camphor–SO_3Na	17	100	62
3	$[Rh(COD)Cl]_2$	$C_6H_5CO_2Na$	17	100	61
4	$[Rh(COD)Cl]_2$	KI	72	100	0
5	$[Rh(COD)Cl]_2$	$AgBF_4$	4	90	65
6	$Rh(CO)_2Acac$	–	20	81	11
7	$[Rh(COD)OAc]_2$	–	17	100	67
8	$Rh(COD)_2BF_4$	Camphor–SO_3Na	17	100	63

[a] Conditions: 0.025 mmol of dimeric Rh-precursor, 0.055 mmol of **1**, 0.55 mmol of added anion, stirring for 1 h, than 5 mmol of substrate was added, 20 ml of MeOH, RT, 70 bar H_2.
[b] All products had the R-configuration.

rate of the reaction seems to be higher. Changing the anion from chloride to acetate also had no influence on enantioselectivity. These results disprove the theory that the extraordinary mono-sulfonated ligand effect can be attributed to a simple anion effect.

4. Conclusion

We have shown that use of monosulfonated BDPP (**1b**) in the rhodium catalyzed hydrogenation of **2** leads to the amine product in 94% ee, whereas use of the bissulfonated ligand **1c** gave practically racemic product. This peculiar effect is not due to steric reasons, as the ligand is a 1:1 mixture of diastereomers. Difference in electron density at the two phosphorus atoms is also not involved, as hydrogenation of **2** using the trissulfonated ligand **1d** proceeded in very low enantioselectivity. The effect is not general because in the hydrogenation of N-acetamidocinnamic acid (**4**) and methyl ester (**6**) enantioselectivity decreased with increasing degree of sulfonation. Hydrogenation of dimethyl itaconate (**8**) showed a minor mono-sulfonation effect. Possibly the effect is limited to monodentate substrates only. The effect is also not due to the fact that the complex between rhodium and **1b** is cationic nor is there an anion effect involved.

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