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Asymmetric Hydroformylation of Styrene Using a Rhodium Catalyst with BDPP as the Chiral Ligand

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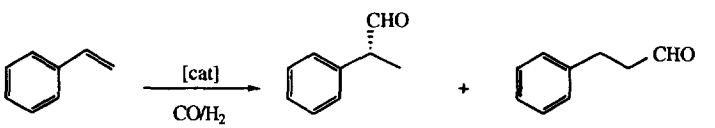
Abstract: Asymmetric hydroformylation of styrene is performed using the available rhodium $[Rh(\mu\text{-}OMe)(COD)]_2$ complex with BDPP as the chiral auxiliary ligand. The enantiomeric excesses observed heavily depend on the excess of diphosphine used and ee's of up to 60 % are achieved. The influence of different P and T conditions is also discussed.

INTRODUCTION

Much effort has been devoted in recent years to the study of catalytic systems based on platinum and rhodium complexes which could provide higher regio and stereoselectivity in the asymmetric hydroformylation of styrene **1** (scheme 1) and other related substrates.[1, 2]

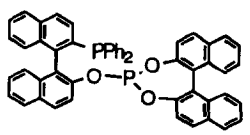


1 **2** **3**

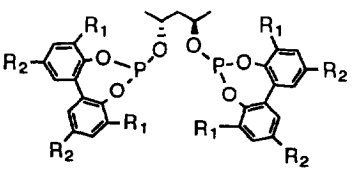
Scheme 1

Recently, hydroformylation catalyst precursors based on $[Rh(acac)(CO)_2]$ modified with phosphine-phosphite **4**[3] or diphosphites **5**[4] and [Rh(cod)(diphosphinites)][5] have provided ee's of between 50 and 96 % in the hydroformylation of styrene and other olefins as well as excellent chemo and regioselectivity in same cases.

In practically all Pt or Rh chiral catalysts, bidentate phosphorus chiral ligands, whether or not they have C_2 symmetry, are present in the complex or are added to the catalytic solution.



4 BINAPHOS

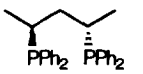


5 DIPHOSPHITES

5a: R_1 = t-Bu; R_2 = t-Bu
5b: R_1 = OMe; R_2 = OMe

6 DIPHOSPHINITES

6a: Ar = 3,5-$(CF_3)_2C_6H_3$



7 BDPP

Figure 1

The structures in solution of selective rhodium catalyst modified with diphosphine ligands have been reported by other authors[6,7] and selectivity has recently been proved to depend on the structure of different modified diphosphines and diphosphites.[7,8] It was shown that bidentate phosphorus ligands form trigonal bipyramidal hydridorhodium complexes which should be active catalysts in the hydroformylation reaction. It is actually assumed that these pentacoordinate intermediates are significantly involved in the stereoselectivity of the reaction.[1, 2]

Furthermore, structural and NMR studies have shown the bite angle of the diphosphine is related to the formation of an equatorial-equatorial or equatorial-axial pentacoordinate intermediate species and the influence this has on the regioselectivity and enantioselectivity of the hydroformylation reaction.[3,9]

In addition, it is generally accepted that several different species may coexist under hydroformylation conditions. In order to increase the chemo-, regio- and stereoselectivity of the reaction, the relative concentration of the preferred species should be maximised.[2] For this reason, the formation of a single catalytic species has also been suggested as one of the most important factors for obtaining high enantioselectivity.[3,10]

We have recently reported that the starting rhodium complexes also influence the enantioselectivity. Thus, taking the catalytic precursor systems prepared by adding (+)-BDPP (**7**) to the dinuclear dithiolate complexes $[Rh_2(\mu\text{-}S(CH_2)_nS)(COD)_2]$ (n = 2, 3 and 4) in the hydroformylation of styrene, P/Rh molar ratio = 2, 94 % in 2-phenylpropanal was obtained, together with enantiomeric excesses up to 42 % (S); meanwhile, under the same conditions, the precursor system $[Rh_2(\mu\text{-}OMe)(COD)]_2$/(+)-BDPP provides a lower ee (5 %).[11]

In this report we show that a simple diphosphine such as BDPP provides higher ee than previously reported for simple diphosphines, the determining factor being the phosphoros rhodium ratio. The latter controls the formation of the predominant catalytic species in particular reaction conditions.

RESULTS AND DISCUSSION

Initially we tested the addition of (+)-BDPP to the $[Rh(\mu\text{-}OMe)(COD)]_2$ complex with a P/Rh ratio = 2. This system is active in the hydroformylation of styrene at 5 bars of CO/H_2 pressure and 65 °C and provides a 88 % conversion into aldehydes in 7 hours with a regioselectivity in 2-phenylpropanal of 77 %. However the enantioselectivity of this system is practically zero (Table 1, entry 1). In the same conditions, 5 bars and 65 °C, but using a P/Rh ratio = 4, the $[Rh_2(\mu\text{-}OMe)(COD)_2]$/BDPP system provides a 90 % conversion into aldehydes in 7 hours with a regioselectivity in 2-phenylpropanal of 94 % and an ee of 53 % (S) (entry 2).

At the same temperature and P/Rh ratio, similar results are obtained by increasing the CO/H_2 pressure to 10 bars and an ee of 56 % is achieved with the same regioselectivity (entry 3). The influence of the P/Rh ratio on the selectivity should be pointed out, since a P/Rh ratio = 2 does not enable a significant ee to be obtained either at 10

bars (entry 4) or at 30 bars (entry 5). This suggests that the catalytic species providing enantioselectivity formed require the presence of two molecules of diphosphine per rhodium in the precursor system. On the other hand, the regioselectivity in 2-phenylpropanal is lower at this P/Rh ratio = 2 (entries 4 and 5).

Table 1. Styrene Hydroformylation with $[Rh(\mu\text{-}OMe)(COD)]_2$/(+)-BDPP as Catalyst Precursor System at 65°C.[a]

Entry	P/Rh	Pressure (bar)	Time (h)	Conv.(%)[b]	2/3 (%)	ee(%)[c]
1	2	5	7	88	77/23	< 1 (R)[d]
2	4	5	7	90	94/6	53 (S)[d,e]
3	4	10	7	92	94/6	56 (S)[d,e,f]
4	2	10	12	100	84/16	2 (S)[e,f]
5	2	30	12	100	90/10	5 (R)[e,f]
6[g]	2	10	1.5	90	84/16	17 (S)[d]
7	8	10	7	76	95/5	45 (S)[d]
8	8	30	24	92	94/6	48 (S)[e,f]

[a]Reaction conditions: Solvent = THF; CO/H_2 = 1/1; Substrate /precursor = 200. [b] Conversion into aldehydes. [c]Absolute configuration in parentheses; [g] CO/H_2=1/4, 6% hydrogenation products. Enantiomeric excess determined by GC using the [f]alcohols, [d]acids; [e]Enantiomeric excess determined by ^1H NMR using $[Eu(hfbc)_3]$.

Since the carbon monoxide and the diphosphine ligand compete in coordination and afford different species,[1, 2] decreasing the CO pressure could lead to a species with the diphosphine coordinated to the metal. To this end, an experiment was performed using P/Rh = 2 and CO/H_2 pressure ratio = 1/4 (entry 6). In these conditions the system shows higher activity, 90% conversion into aldehydes in 1.5 hours, together with a regioselectivity in 2-phenylpropanal of 84 %. The ee, 17 % (S), increases in comparison with experiment 4, where under the same conditions but CO/H_2 ratio = 1, the ee was only 2 % (S). However 6 % of a hydrogenated product is also obtained. No further improvement is obtained when the P/Rh ratio is increased to 8 at 10 bars. In fact the ee decreases to 45 % (S) (entry 7). At 30 bars the regioselectivity in 2-phenylpropanal is maintained and the ee obtained was 48 % (S) (entry 8).

It is known that, in general, better selectivities are obtained by decreasing the temperature.[7] The results obtained in the hydroformylation of styrene using the $[Rh_2(\mu\text{-}OMe)(COD)_2]$/(+)-BDPP system, P/Rh ratio = 4 at 40 °C are shown in Table 2. As was expected, lower activities were obtained when the temperature was decreased. 96% of 2-phenylpropanal and an ee of 60 % was obtained at 30 bars of CO/H_2 pressure (entry 9). To avoid possible racemization processes we performed the reaction in $HC(OEt)_3$ with added pyridinium *para*-toluensulphonate (PPTS) so as to direct obtain diethyl acetals,[12] but there was no improvement in the ee in this case (entry 10).

Increasing the CO/H_2 pressure at 50 bars, gives an ee of 53 % (S) with the same regioselectivity in 2-phenylpropanal (entry 11). In experiment 12, where the CO/H_2 ratio = 1/4, there was no hydrogenation and the ee increased slightly in comparison to experiment 11.

However, at 80 bars the ee decreases to 35 % (S) (entry 13) probably due to the presence of species where diphosphine ligands are removed by carbon monoxide, that is to say, different species are present in the reaction mixture. Using another typical rhodium precursor such as $[Rh(acac)(CO)_2]$ the same results are obtained when (+)-BDPP is used in the same P/Rh ratio. For purposes of comparison, similar experiments were carried out in the same hydroformylation conditions using (+)-DIOP and (+)-BINAP in P/Rh = 4 as chiral diphosphines (Table 3, entries 13 and 14). However, lower ee's were obtained.

Table 2. Styrene Hydroformylation with $[Rh(\mu\text{-}OMe)(COD)]_2$/(+)-BDPP as Catalyst Precursor System at 40°C[a]

Entry	P/Rh	Pressure (bar)	Time (h)	Conv.(%)[b]	**2/3** (%)	ee(%)[c]
9	4	30	24	12	96/4	60 (S)[d]
10[e]	4	30	49	13	96/4	50 (S)[d]
11	4	50	73	24	96/4	53 (S)[f]
12[g]	4	50	24	13	96/4	57 (S)[d,f]
13	4	80	26	5	95/5	35 (S)[d]

[a]Reaction conditions: Solvent = THF; CO/H_2 = 1/1; Substrate/precursor = 200. [b]Conversion into aldehydes. [c]Absolute configuration in parenthesis. [e]using triethyl orthophormyate as solvent. [g]CO/H_2 = 1/4. Enantiomeric excess determined by GC using the [d]alcohols,[f] acids.

Table 3. Styrene Hydroformylation Using Different Rhodium Catalyst.[a]

Entry	Precursor	L	Pressure (bar)	t (°C)	Time (h)	Conv. (%)	**2/3** (%)	ee (%)	Ref.
14[b]	$[Rh(\mu\text{-}OMe)(COD)]_2$	(+)-DIOP	10	65	7	94	61/39	12 (S)	-
15[b]	$[Rh(\mu\text{-}OMe)(COD)]_2$	(+)-BINAP	10	65	7	63	91/9	25 (S)	-
16[c]	$[Rh(acac)(CO)_2]$	(R,S)-**4**	100	60	43	>99	88/12	94 (S)	3
17[d]	$[Rh(acac)(CO)_2]$	(R,R)-**5a**	9	25	5	21	96/4	68 (S)	4a
18[d]	$[Rh(acac)(CO)_2]$	(R,R)-**5b**	40	25	n.i.	n.i.	98/2	90 (S)	4b
19[e]	[(**6a**)Rh(COD)BF_4]	**6a**	123	n.i.	n.i.	62	96/4	24	5

[a]n.i.= not indicated; [b]Solvent: THF; CO/H_2 = 1/1; P/Rh = 4; substrate/precursor =200; [c]solvent: benzene (solvent/substrate ratios 0.5-1); CO/H_2 = 1/1; substrate/[Rh] ratio = 2000; ligand/[Rh] ratio 2.0-4.0.; [d]solvent: toluene; CO/H_2 = 1/1; substrate/catalyst molar ratio = 421; ligand/[Rh] ratio 8; [e]solvent: toluene; CO/H_2 = 1/1; ligand/[Rh] ratio 4, reaction rate (g. moles/liter/hr) = 0.11; ligand/Rh ratio 4.

Furthermore, comparing with the most relevant results obtained using rhodium catalysts reported in the literature (Table 3, entries 16-19) only ligands **4** and **5** containing biphenyl or binaphtyl substituents provided better ee's. Thus, using the complex containing the phosphine-phosphite **4**, excellent enantioselectivities were obtained at high pressure and moderate temperature (entry 16). High enantioselectivies had also been reported using the diphosphite **5**, at low temperature, although in this case, the conversion considerably decreased. The sugar diphosphinite derivative **6** that provided high ee's in hydroformylation of vinyl naphthalene was less efficient in styrene hydroformylation.

CONCLUSIONS

In conclusion, in the hydroformylation of styrene, catalytic precursors based on available rhodium systems using a structurally simple diphosphine such as BDPP provide a regioselectivity in 2-phenylpropanal of up to 95% with ee's of up to 60% being the appropriate P/Rh ratio 4 in this case. Thus, a promising asymmetric

induction can be obtained by a fairly simple ligand used in the relevant P/Rh ratio in order to provide a predominant intermediate species. Studies on the scope and mechanistic aspects of this catalytic system are in progress.

EXPERIMENTAL

The diphosphines (+)-BDPP, (+)-DIOP and (+)-BINAP, and the [Eu(hfbc)$_3$] chiral shift reagent were of commercial origin and they were used without further purification. The [Rh(μ-OMe)(cod)]$_2$ complex was prepared using standard methods[13]. Solvents were distilled and deoxygenated before use. Proton NMR spectra were measured on a Varian 300 MHz spectrophotometer, and chemical shifts are quoted in ppm downfield with $SiMe_4$ as the internal standard. Gas chromatographic analyses were carried out on a Hewlet-Packard Model 5890 A gas chromatograph with flame ionization detector using a 25-m capillar column (Ultra 2). Enantiomeric excess was measured by GC on the same equipment using a 50-m capillar column (FS-Cyclodex β-I/P). Hydroformylation experiments were carried out in an autoclave with a magnetic stirring. The catalytic solution was contained in a glass vessel. The inside of the autoclave cap is Teflon-covered to avoid direct contact of the solution with stainless steel. Constant temperature was maintained by circulation of water through a double jacket.

Standard catalysis experiment-. A solution of the substrate (20 mmol), the catalysts precursor (0.1 mmol) and the phosphorus compound in 15 mL of the anhydrous tetrahydrofuran were introduced into the evacuated autoclave. The gas mixture was introduced and the system was heated. When thermal equilibrium was reached, the gas mixture was introduced until desired pressure was reached. After the reaction time, the autoclave was cooled to room temperature and depressurized. Conversions and regioselectivities were determined by GC analysis of crude samples without the addition of any external standard. Enantiomeric excess was measured by GC and by ^{1}H NMR.

Enantiomeric excess measurements-. Enantiomeric excesses were measured by three different methods.

GC with a chiral column on the alcohols obtained by reduction of the product aldehydes.

After the catalytic run, 2 mL of the final catalytic solution was added drop by drop to a stirred suspension of lithium aluminium tetrahydride (110 mg) in 5 mL of anhydrous tetrahydrofuran. After 5 minutes, methanol was added until bubbling stopped. Aluminium salts were removed by filtration through Celite. The filtrate was evaporated until dry, dissolved in diethyl ether (30 mL), washed with sulphuric acid (10 %) (3x15 mL), dried over magnesium sulfate distilled and analyzed by GC.

GC with a chiral column on the acids obtained by oxidation of the product aldehydes .[14]

After the catalytic run, 2 mL of the final catalytic solution was diluted with an aqueous 1.25 M potassium phosphate buffer solution (10 mL) adjusted to a 5 pH value and to the resulting solution was added, with vigorous stirring, an aqueous 1M $KMnO_4$ solution (10 mL) at room temperature. After 30 minutes, the oxidation was quenched by the addition of a saturated solution of Na_2SO_3 and the resulting pH of the mixture was adjusted to 3 with cold dilute HCl to dissolve the colloidal MnO_2. The usual extractive workup provided the carboxylic acids which after distillation were analyzed by GC.

^{1}H NMR using [Eu(hfc)$_3$] as a chiral shift reagent .[15]

After the catalytic run, 0.2 mL of the catalytic solution was evaporated to dryness and dissolved in C_6D_6. Small portions of [Eu(hfc)$_3$] were added and the ^{1}H NMR were recorded until neat splitting of the signal for the formyl proton.

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