Phosphite and thiourea ligand synergy for rhodium catalyzed enantioselective hydroformylation of styrene

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Abstract

New non-C_2-symmetric chiral diphosphites have been synthesized and used as ligands in the rhodium catalyzed enantioselective and regioselective hydroformylation of styrene. A synergistic effect improving both activity and enantioselectivity is observed when a chiral dithiourea is introduced as co-ligand in the Rh-diphosphite catalytic system.
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1. Introduction

Hydroformylation is one of the largest-volume processes of organometallic catalysis [1,2] and is therefore widely studied [3–5]. Moreover, enantioselective hydroformylation of styrene derivatives promises a shortcut access to anti-inflammatory drugs yielding chiral 2-arylpropionic aldehydes, which can be oxidized to pharmaceutically active 2-arylpropionic acids like Naproxen or Ibuprofen [6].

However, efficient catalysts for this reaction are still rare since it requires good chemo, regio and enantioselectivities (Scheme 1). The first example of a highly enantioselective catalyst was reported by Takaya and co-workers 12 years ago and it is based on Rh-BINAPHOS [7]. Many studies on this phosphine-phosphite system lead to a very active and selective olefin hydroformylation catalyst which can be used solvent free in supercritical CO_2 media [8,9] or recovered when polystyrene-supported [10]. In the case of styrene [10] this catalyst allows an enantiomeric excess of 95 and 99% conversion with an *iso*-selectivity of 92.5%.

Some rhodium-diphosphite catalysts have been prepared for the enantioselective hydroformylation of styrene based on (2R, 4R)-pentane-diol with C_2-symmetry [11–13] or on tunable fura-noside backbones [14–16]. In these derivatives, all of the chiral centres are not involved in the enantioselective process, but they are sometimes detrimental to it. The rhodium-diphosphite catalytic systems require low temperature and pressure to afford high enantiomeric excesses what is detrimental to their activity. Best results were obtained with [Rh(acac)(CO)$_2$] and a ligand derived from D-(+)-glucose: 90% ee with 98.6% yield on 2-phenylpropanal for a styrene conversion of 83% (48 h at 20 °C, TOF = 18 mol styrene. Rh^{-1} h^{-1}). Activity can be increased by changing temperature (TOF = 174 mol styrene. Rh^{-1} h^{-1} at 40 °C), but enantioselectivity drops to 78% [17]. Claver and co-workers reported that *tert*-butyl groups in the bisphenol moieties also have an important effect on asymmetric induction [18].

As in many other fields of asymmetric catalysis, the use of other heteroatoms such as O, N or S has been investigated for hydroformylation of styrene [3–5,19,20]. The only non-phosphorinated compounds developed for this purpose are indeed sulphur containing ligands: thiols, thioethers and thioureas [5,21–24]. Some enantioselective examples have been reported but ee values remain modest and conversions rather low.

Claver and co-workers prepared chiral thioethers-phosphites analogues to their best furanoside diphosphites. These novel P,S-ligands were used in rhodium catalyzed styrene hydro-formylation and led to excellent activities and regioselectivities, but no significant enantioselectivities were detected [25].

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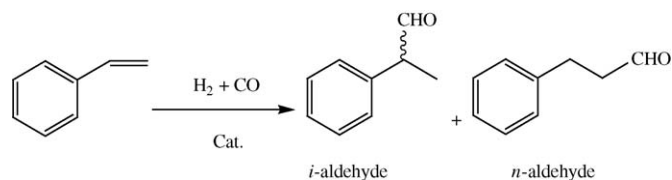
Scheme 1. Hydroformylation of styrene.

Recently, Gladiali et al. reported the use of an heterobidentate P, S version of BINAP in asymmetric catalysis [26,27]. The in situ Rh catalyst formed from the BINAPS (*R*)-methyl sulfide lead to a complete styrene hydroformylation, 96% of isoaldehyde but only 14% ee [26].

Diphosphites are selective ligands for the rhodium catalyzed hydroformylation, but their activities should be improved. The combination of P and S heterodonor ligands with rhodium give highly active catalysts for this reaction, but the obtained chiral inductions are low with the reported systems. It is worthy to evaluate if there is any synergetic effects between chiral diphosphites and chiral thioureas. This is the goal of the present study in which we first describe the synthesis of novel chiral diphosphites and their use in rhodium catalyzed styrene hydroformylation. The effect of chiral thiourea ligands on the rhodium-diphosphite catalyst is then reported.

2. Experimental

2.1. General procedures

All the organic and organometallic reagents are pure commercial products. The solvents are reagent grade and are dried and distilled by standard techniques before use. Melting points

(m.p.), uncorrected, are determined with an Electrothermal 9100 apparatus. Elemental analyses are obtained from the Service Central d'Analyse of the CNRS (Solaize). High-resolution mass spectra: HR liquid secondary ionisation mass spectrometry (LSIMS: Thioglycerol), HR CIMS (Isobutan) and were carried out on a Finnegan MAT 95×L by the UCBL Centre de Spectroscopie de Masse. $[\alpha]_D$ were determined with a Perkin-Elmer 241 polarimeter (l = 1 dm; 25 °C; concentration *c* in g/100 mL). ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC-200 (200.13 MHz for ^1H, 50.32 MHz for ^{13}C); δ values are given in ppm and *J* in Hz. GC analysis (styrene conversion, aldehyde yields and enantioselectivities) were determined with a Shimadzu (SE-54) chromatograph equiped with a chiral column (Supelco β-DEX-225, 60 m, i.d. 0.25 mm), using decane as internal standard.

2.2. General procedure for the synthesis of diphosphite ligands

The chiral diphosphites **1** and **2** were synthesized from (*S*)-methyl or phenyl-1,3-butanediol and the corresponding phosphochloridite (Scheme 2), which was prepared according to the procedure published by van Leeuwen and co-workers [13]. The diols (1 mmol) were dissolved in THF (25 mL) and triethylamine (2.5 mL) and added dropwise to a phosphochloridite (5 mmol) solution in THF (25 mL), at 0 °C. The reaction mixture was heated to reflux overnight. The resulting triethylamine salts were filtered off. Evaporation of the solvent gave white foams, which were purified by washing several times with acetonitrile to give white solids which were then dried under vacuum for 24 h. The diphosphites were obtained in good yields (>70%).
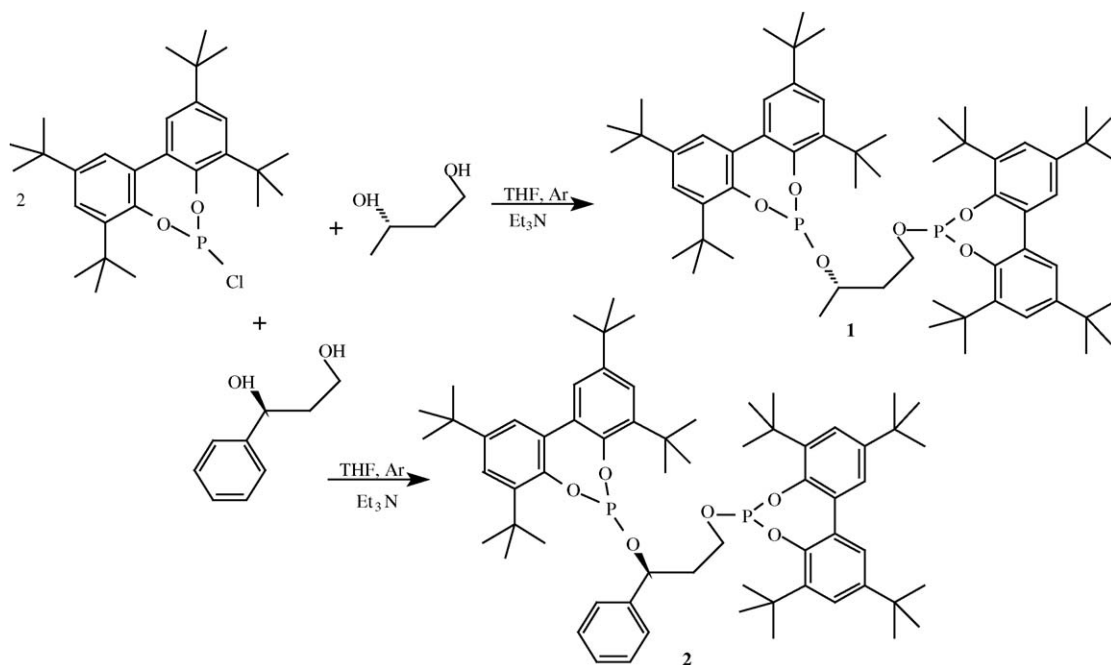
Scheme 2. Diphosphite synthesis.

2.2.1. Synthesis of (S)-1,3-bis-[((2,4,8,10-tetra-tert-butyl)-dibenzo-[d,f][1,3,2]-dioxa-phosphepin-6-yl)oxy]-butane 1

White solid (82% yield); m.p. 192 °C. $[\alpha]_D = -6.3$ ($c = 2.73$, $CHCl_3$). FAB-MS (NBA) $(M + Cu)^+$: 1030.1. ^1H NMR ($CDCl_3$) δ (ppm): 7.5-7.4 (m, 4H, arom.), 7.2-7.1 (m, 4H, arom), 4.7-4.5 (m, 1H, CHO), 4.0-3.8 (m, 2H, CH_2O), 2.0-1.6 (m, 2H, CH_2), 1.6-1.3 (m, 72H, ^tBu), 1.19 (d, 3H, $J = 6.4$, CH_3). ^{13}C $\{^1H\}$ NMR ($CDCl_3$) δ (ppm): 146.3; 146.2; 146.1; 139.9; 139.8; 139.7; 132.6; 132.4; 126.5; 124.2; 124.1 (arom); 70.0 (CHO), 61.2 (CH_2O), 39.0 (CH_2), 35.3; 34.6; 31.5; 31.2; 31.0; 30.9 ($C(CH_3)_3$), 22.1 (CH_3). $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ (ppm): 145.6; 136.0. Anal. Calcd. for $C_{60}H_{88}O_6P_2$ (967.30): C, 74.50; H, 9.17; P, 6.40. Found: C, 73.61; H, 9.18; P, 6.40.

2.2.2. Synthesis of (S)-1-phenyl-1,3-bis-[((2,4,8,10-tetra-tert-butyl)-dibenzo[d,f][1,3,2]-dioxaphosphepin-6-yl)oxy]-propane 2

White solid (70% yield); m.p. 120 °C. $[\alpha]_D = +4.0$ ($c = 1.0$, CH_2Cl_2). FAB-MS (NBA) $(M + Cu)^+$: 1091.9. ^1H NMR ($CDCl_3$) δ (ppm): 7.8-7.0 (m, 13H, arom.), 5.4-5.2 (m, 1H, CHO), 4.9-4.7 (m, 2H, CH_2O), 4.0-3.7 (m, 2H, CH_2), 1.6-1.3 (m, 72H, ^tBu). ^{13}C $\{^1H\}$ NMR ($CDCl_3$) δ (ppm): 146.3; 146.2; 146.1; 139.9; 139.8; 139.7; 132.6; 132.4; 129.0; 128.9; 128.8; 128.7; 128.3; 128.2; 127.8; 127.3; 127.2; 127.1; 126.9; 126.7; 126.4; 125.7; 124.1 (arom), 70.8 (CHO), 62.0 (CH_2O), 40.0 (CH_2), 35.2; 35.1; 34.5; 34.4; 33.6; 33.4; 31.5; 30.9 ($C(CH_3)_3$). ^{31}P $\{^1H\}$ NMR ($CDCl_3$) δ (ppm): 144.7; 134.0. Anal. Calcd. for $C_{65}H_{90}O_6P_2$ (1029.37): C, 75.84; H, 8.81; P, 6.02. Found: C, 75.49; H, 8.76; P, 5.99.

2.3. General procedure for the synthesis of dithiourea ligands 3–5

The chiral thiourea ligands **3–5** were easily prepared by reaction of chiral amine with stoichiometric amounts of the corresponding isothiocyanate (Scheme 3). Each thiourea was obtained in more than 90% yield [24].

2.4. Catalytic tests

In a typical experiment, the catalysts were prepared in a Schlenck tube just before the hydroformylation experiment by mixing for 1 h [Rh(acac)(CO)$_2$] with the diphosphite at room temperature in dry dichloromethane (4–16 mL). Then, thiourea is dissolved in the solution (no precipitate and no insoluble particles are observed) and the whole mixture is transferred under argon into a 25 mL purged stainless-steel autoclave. Styrene (2 mL) is added and the autoclave is sealed, purged with H_2 and pressurized to the appropriate initial pressure with CO–H_2 (1:1). The autoclave is heated at 40 °C and the reaction mixture is stirred for 24 h. The autoclave is then cooled and depressurised. The reaction mixture is transferred from the autoclave. Conversions, enantioselectivity and composition of the reaction mixture (i/n: branched/normal) are determined by analysing this final solution in a gas chromatography using chiral column (Supelco β-DEX-225, 60 m, i.d. 0.25 mm). Decane is used as an internal standard. (R) and (S) enantiomers of 2-phenyl-propanal were determined with a reduced sample (with LiAlH$_4$) which was compared to enantiopure authentic samples of alcohols (Supelco β-DEX-225, 60 m, i.d. 0.25 mm). The NMR spectrums of the alcohols thus obtained are identical to those of the commercial products (Aldrich).

3. Results and discussion

The catalysts were always prepared in situ by adding an excess of diphosphite ligand **1** or **2** to the metallic precursor, [Rh(acac)(C$_2$H$_4$)$_2$] and styrene hydroformylation was carried out under mild conditions (40 °C, 20–60 bar CO/H_2). Selected results are reported in Table 1.

In all the tests, an excellent chemoselectivity (>99%) was noted since only traces of hydrogenated byproduct were detected. Very good regioselectivities are also observed with i/n ratios upper than 97/3, except in toluene. The solvent has a crucial role in styrene hydroformylation with Rh-diphosphite **1** catalyst. Even if better conversion was obtained in toluene (entry 1), changing this solvent by THF (entry 2) and then by CH$_2$Cl$_2$ (entry 3) afforded a simultaneous increase in isoselectivity and enantioselectivity. Conversion could be enhanced with longer reaction times (entry 3). Encouraging but moderate ee values were observed for Rh-**1** and Rh-**2** catalysts when ligands 1 or 2 are used in large amounts (30% ee has been observed for **1**/Rh = 2). Use of higher H_2/CO pressures led to a neat decrease in activity but did not affect significantly chemo, regio nor enantioselectivities (entry 6). The formation of stable carbonyl compounds should then be favoured to the detriment of the active species.
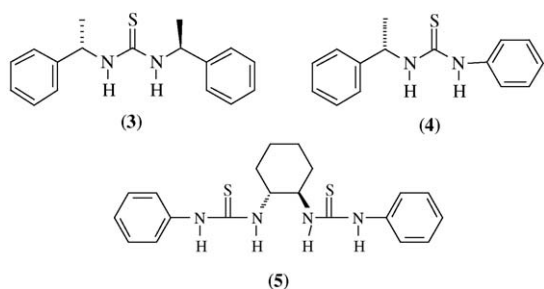
Scheme 3. Chiral thiourea ligands.

Table 1
Styrene hydroformylation catalyzed by rhodium diphosphite **1** or **2** species

Entry	L*	P (bar)	Solvent	Time (h)	% Conversion	i/n	% ee
1	**1**	20	Toluene	24	81	85/15	17 (R)
2	**1**	20	THF	48	25	97/3	30 (R)
3	**1**	20	CH$_2$Cl$_2$	48	88	98/2	43 (R)
4	**1**	60	CH$_2$Cl$_2$	24	25	99/1	40 (R)
5	**2**	20	CH$_2$Cl$_2$	24	50	99/1	45 (S)
6	**2**	60	CH$_2$Cl$_2$	24	28	98/2	43 (S)

Styrene/L*/Rh = 5000/5/1; [Rh(acac)(C$_2$H$_4$)$_2$]: 4.10^{-6} mol.l^{-1}; H_2/CO = 1/1; $T = 40$ °C. Only traces of ethylbenzene (<1%) were detected in all cases.

Table 2
Styrene hydroformylation using Rh-**1** and n equivalents of thiourea **3–5**

Entry	Thiourea (n)	n/Rh	Time (h)	% Conversion	i/n	% ee (R)
7	**3**	1	24	26	99/1	45
8	**3**	1.5	24	27	98/2	46
9	**3**	1.5	160	100	96/4	40
10	**3**	2	24	9	98/2	43
11	**4**	1	24	49	99/1	46
12	**4**	1	160	95	98/2	42
13	**4**	2	24	37	99/1	44
14	**5**	1	48	94	99/1	52

Styrene/L*/thiourea/Rh = 5000/5/n/1;   [Rh(acac)$(C_2H_4)_2$]: 4.10^{-6} mol.l^{-1} H_2/CO = 1/1; $P = 20$ bar; $T = 40\,°C$ in CH_2Cl_2.

Opposite enantioselectivity is observed for Rh-**1** and Rh-**2** catalysts since they lead to 45% ee of (*R*) and (*S*) 2-phenyl-propanal, respectively. If we consider the relative position of both phosphite moieties in ligands **1** and **2** we notice that they are also inverted: in compound **1** phosphite group on C-1 atom is pointing back while in compound **2** the same group is pointing front. Final configuration of C-1 atom is (*S*) in both cases because the methyl group in **1** is replaced by a phenyl group in **2**. It is noticeable that the bulkier group onto C-1 atom did not modify the enantioselection.

In order to increase the enantioselectivities induced by the diphosphites **1** and **2** ligands, we examined the effect of a co-ligand. As chiral thioureas were encouraging ligands for rhodium catalysis hydroformylation of styrene [24], we chosed to use them as the co-ligand. Thioureas **3**, **4** and **5** were thus tested in various co-ligand/rhodium molar ratios, while diphosphite ligand **1**/rhodium molar ratio remained unchanged. Since the two diphosphites (**1** and **2**) gave the same enantioselectivity we studied the effect of addition of thioureas for the biphosphite **1** only.

In our previous studies, we have shown that the rhodium complex formed in situ with thiourea **3** (Rh-**3**) can act as hydroformylation catalyst in the same conditions (40 bar CO/H_2 = 1/1, 40 °C) and observed that asymmetric induction appears only for **3**/Rh = 2 (16% ee, 18% conversion in 18 h for styrene/Rh = 350/1). We found that Rh-**4** lead to 24% ee (*S*) with low activity for **4**/Rh = 1 (18% ee (*S*), same ratios) and no activity for **4**/Rh = 2. We attributed this to rearrangement of rhodium-thiourea precursors in 'naked rhodium species' and stable inactive coordinatively saturated complexes with two molecules of thiourea for one rhodium atom since dithiourea associated to rhodium results in inactive catalysts too. This transformation is slowered by the bulkiness of the thiourea (**3**, slow; **4**, faster) [24].

Even if the amount of diphosphite to rhodium is high (typically 5), a few 'naked rhodium species' appear. We expected to poison them with the excess of free thiourea in the reaction media, so that the enantioselectivity increase with a loss in activity. The experimental results are reported in Table 2.

For a total pressure of 20 bars and a reaction time, 24 h, the presence of thiourea **3** in ratio from 1 to 1.5 lead to a very low enantioselectivity enhancement (entry 7 and 8 compared to entry 3). Complete conversion is obtained in 160 h (entry 9) with a significant loss in regio- and enantioselectivity. During the

reaction, the reactor was repressurized three times to maintain the global pressure constant at 20 bars. When an excess of thiourea **3** is used in the presence of diphosphite (entry 10), the activity seriously decreases and the enantioselectivity detected for this test is the same that for the catalyst formed without co-ligand. Thus, thiourea **3** (C_2 symmetry) has no influence on the enantioselectivity.

Another thiourea **4** with C_1 symmetry has been also tested. The addition of this mono-thiourea **4** does not change significantly the results (entry 11 and 13). As for thiourea **3**, more than 160 h are needed to reach a total conversion without neat loss of enantioselectivity (entry 12). Thus, monothiourea **3** (C_2 symmetry) or **4** (C_1 symmetry) have no influence on the enantioselectivity and do not stabilize the rhodium-diphosphite catalytic system efficiently, but they act as rhodium poisons.

Finally, the addition of di-thiourea **5** as co-ligand is tested. This test shows clearly an increase in both activity (94% compared to 88%) and enantioselectivity (52% compared to 40%, entries 14 and 3) with an improved regioselectivity. When a dithiourea **5** is used in absence of phosphite ligand under the same conditions the system is then completely inactive. This shows that the phosphite ligands have a crucial role in this reaction and that dithiourea does not act as two mono-thiourea molecules. In order to determine precisely the role of thiourea associated to rhodium-phosphite complexes, in situ FT-IR are under study.

4. Conclusion

Moderate enantioselectivity (43% ee) was observed, but these results are very encouraging since only one stereogenic carbon atom (C-1) is responsible for the enantioselection: opposite enantioselectivity is observed for Rh-**1** and Rh-**2** complexes. Synthesis of more enantioselective ligands should be performed, but this is very difficult, although some features are known, such as replacing tBu groups by methoxy groups [18]. The addition of mono-thioureas does not improve the enantioselectivity of the reaction or the activity of the rhodium-diphosphite catalyst. Di-thiourea **5** instead, shows the most important effect as a co-ligand, improving ee up to 52% and conversion up to 94%. Only few hydroformylation systems are able to give more than 50% ee with such activity and selectivities. This result can suggest the opportunity to use dithioureas as selective poisons to improve the catalytic activity of other rhodium-phosphite catalysts. A series of chiral diphosphites also containing one sulfur atom (P∩P∩S) should be considered too.

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