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Aryloxypropanoic herbicides by asymmetric hydroformylation catalyzed by rhodium carbonyl complexes modified with phosphorus ligands

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Abstract

Three aryl vinyl ethers have been subjected to enantioselective Rh(I) catalyzed hydroformylation using diphosphites **10** and **11** described in the literature and diphosphites **12–16** synthesized in our laboratories as ligands. All these ligands afforded in most cases 80–90% yields 2-aryloxypropanals as valuable precursors of the very selective herbicides, 2-aryloxypropanoic acids. The same unsaturated substrates have been also hydroformylated in the presence of Rh complexes with commercially available ferrocenylphosphines **17–19**: these catalytic complexes showed generally satisfactory reaction rates as well as regioselectivities, but in some cases, lower chemoselectivities than those containing diphosphites. The enantioselectivities obtained with all described ligands were rather low (up to 9%).

Keywords: Rhodium carbonyl; Hydroformylation; Herbicides

1. Introduction

In recent years, the interest of synthetic organic chemists towards the preparation of agrochemicals has remarkably increased [1,2]. In particular, the attention of various research groups focused on preparative methods for the preparation of chiral non-racemic pesticides [3,4]. Systematic studies on parameters determining the biological properties of these compounds showed that there is often a strict relationship between absolute configuration of stereomers and biological activity [3,4].

The application of chiral catalysts for the production of enantiomerically pure agrochemicals can play an important role to achieve industrially interesting amounts of these compounds:

–enantioselective cyclopropanation catalyzed by chiral Cu(II) complexes with enantiomeri-

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cally pure Schiff bases became an industrial process in the middle of eighties for the production of pyrethroids [5];

–enantioselective hydrogenation catalyzed by Rh(I) or Ru(II) complexes with various chiral non racemic diphosphine ligands has been recently reported to give various types of agrochemicals with excellent enantiomeric excesses [6,7].

For some classes of agrochemicals the hydroformylation of appropriate substrates catalyzed by the carbonyl rhodium complexes appeared to be a rather convenient route: for example, the preparation of racemic 2-(*p*-chlorophenyl)-3-methylbutanoic acid, the key building block for the insecticide (*S,S*)-*Fenvalerate*, was accomplished by hydroformylation of 2-methyl-1-(*p*-chlorophenyl)propene in 88% yield [8]. The 2-aryloxypropanoic acids, a very important family of selective herbicides, are particularly convenient candidates to be produced by hydroformylation reactions. Only a few experiments describing aryl vinyl ether hydroformylation have been reported [9]: rhodium catalysts are reported to produce high aldehyde yields under standard conditions. In most cases, the regioselectivity of the process is definitely in favour of the formation of 2-aryloxypropanals, which are converted by oxidation into the corresponding acids [9,10].

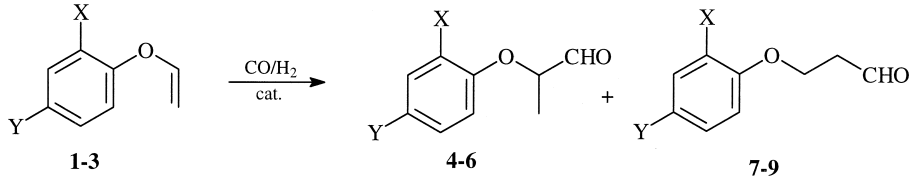
Since herbicidal activity of 2-aryloxypropanoic acids is due to the (*R*)-enantiomer [4], the enantioselective hydroformylation of aryl vinyl ethers appears to be a very attractive preparative route to get the enantiomerically enriched 2-aryloxypropanoic acids.

In this context, we decided to undertake a study of the asymmetric hydroformylation of aryl vinyl ethers using rhodium carbonyl complexes modified with enantiopure sterically hindered diphosphites and ferrocenyldiphosphines. Although phosphitephosphine ligands prepared by Takaya's group [11], whose BINAPHOS is the most popular member, appear to provide highly efficient Rh-catalysts for asymmetric hydroformylation of both arylethenes [12–14] and functionalized olefins [11,15,16], their synthesis involves long and expensive procedures. In contrast, the preparation of both diphosphites and ferrocenyldiphosphines appears to be accessible through much less laborious experimental procedures.

On the other hand, sterically congested chiral phosphites are reported in the recent literature to be effective ligands for Rh(I)-complexes employed in homogeneous asymmetric catalysis [17–28]. Most of these phosphites possess a C_2 symmetry axis. This geometry allows to control the chiral transmission from the metal-complex towards the prochiral center compared to molecules lacking in a such symmetry element [29,30].

Bulky phosphites can be used in homogeneous asymmetric catalysis for the preparation of a wide range of biologically active compounds, because of the tolerance of phosphites for functional groups and because of the mild conditions under which their usually operate [25,26].

The aim of this work was to test a series of new easily available ligands for the enantiose-



1-3 **4-6** **7-9**

1,4,7. X = H, Y = H; **2,5,8**. X = CH_3, Y = Cl; **3,6,9**. X = Cl; Y = Cl

Scheme 1.

lective hydroformylation of aryl vinyl ethers bearing various substituents in the aromatic ring in particular beside to phenyl vinyl ether (Scheme 1), substrates precursors of herbicides like *Mecoprop* [31] and *Dichlorprop* [32] were used in addition. To the best of our knowledge, no examples are appeared in the literature on the hydroformylation of *o*-, *p*-chloro phenyl vinyl ethers.

2. Experimental

2.1. General methods and chemicals

2-*t*-Butylphenol, 4-methoxyphenol, racemic 1,1′-binaphthalene-2,2′-diol (BINOL), (a*R*)-(+)-1,1′-binaphthalene-2,2′-diol ((a*R*)-BINOL), (2*S*,4*S*)-(+)-pentanediol, 1,4:3,6-dianhydro-D-mannitol (isomannide), (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol, $Rh(CO)_2(acac)$, $[Rh(COD)Cl]_2$, phenol, 2,4-dichlorophenol, 2-methyl-4-chlorophenol, 1,2-dibromoethane were of commercial quality and used as purchased (Aldrich). (*R*)-1-[(1*S*)-2-(Diphenylphosphino)ferrocenyl]-ethyldi-*t*-butylphosphine, (*R*)-1-[(1*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine, (*R*)-1-[(1*S*)-2-(dicyclohexylphosphino) ferrocenyl]ethyldiphenylphosphine were of commercial quality and used as purchased (Fluka). 3,3′-Trimethylsilyl-1,1′-binaphthalene-2,2′-diol was prepared according to literature procedures [33,34]. Phosphorus trichloride (PCl_3) was distilled before use and stored under an atmosphere of argon. Triethylamine (Et_3N) was distilled from KOH. All reactions were carried out under a positive pressure of argon. Benzene and THF were freshly distilled from sodium.

^1H NMR and ^{31}P NMR spectra were recorded with a Varian VXR 5000 spectrometer at 299.94 MHz, and 121.42 MHz, respectively. ^{31}P NMR chemical shifts are relative to H_3PO_4 (external standard) in $CDCl_3$. Mass spectra were recorded using a HP 5971 Series Mass Spectrometer. Elemental analyses were performed using an elemental analyser Perkin–Elmer model 240 C. Optical rotations were measured with a Perkin–Elmer mod. 241 spectropolarimeter. The purity of all new compounds was judged to be $>98\%$ by ^1H NMR and ^{31}P NMR spectral determination.

2.2. General procedures for the synthesis of aryl vinyl ethers [35,36]

2.2.1. Phenyl vinyl ether

A mixture of 1,2-dibromoethane (46.1 g, 0.24 mol), phenol (15.0 g, 0.16 mol) and H_2O (80 ml) was well stirred and heated to reflux temperature in a 500-ml three-necked flask equipped with a mechanical stirrer, reflux condenser and dropping funnel. After half an hour a solution of NaOH (8.56 g, 0.21 mol) in H_2O (52 ml) was added dropwise. After the addition of all the NaOH solution, the reaction mixture was refluxed for additional 16 h. After this time, the mixture was cooled, the organic layer was separated and the aqueous phase extracted several times with CH_2Cl_2. The organic extracts were washed with a dilute aqueous NaOH solution, then with H_2O and finally dried over anhydrous Na_2SO_4. After evaporation in vacuo of the solvent and the excess of 1,2-dibromoethane, the resultant crude 1-phenoxy-2-bromoethane (25.7 g) was sufficiently pure (GLC) to be used in the following dehydrohalogenation reaction.

A solution of crude 1-phenoxy-2-bromoethane (25.7 g) in dry benzene (75 ml) was slowly added to a refluxing potassium *t*-butoxide solution over a period of 6 h. After cooling at room temperature, the solution was diluted with H_2O (150 ml) and extracted several times with Et_2O. After the usual work-up, the residue was distilled at reduced pressure: b.p. 54–55°C (10 mmHg) (lit. 152–154°C at 760 mmHg [35]) giving phenyl vinyl ether (12 g, 0.1 mol, 62% overall yield). Mass spectra: EI (70 eV) m/z: 121 $[M+1]^+$, 120 $[M]^+$, 77. ^1H NMR ($CDCl_3$), δ (ppm): 7.45–6.97 (m, 5H,

Ar), 6.71 (dd, $^1J = 13.2$ Hz, $^2J = 6.7$ Hz, 1H), 4.85 (dd, $^1J = 13.2$ Hz, $^2J = 1.6$ Hz, 1H), 4.50 (dd, $^1J = 6.7$ Hz, $^2J = 1.6$ Hz, 1H).

Following the above-described procedure, 2-methyl-4-chlorophenyl vinyl ether and 2,4-dichlorophenyl vinyl ether were prepared in 58 and 64% overall yield, respectively.

2.2.1.1. 2-Methyl-4-chlorophenyl vinyl ether. B.p. 92°C at 5 mmHg (lit. 107°C at 22 mmHg [35]); mass spectra: EI (70 eV) *m/z*: 170 $[M + 2]^+$, 168 $[M]^+$, 153, 139, 133, 127. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.30–6.83 (m, 3H, Ar), 6.59 (dd, $^1J = 15.8$ Hz, $^2J = 6.8$ Hz, 1H,), 4.63 (dd, $^1J = 15.8$ Hz, $^2J = 1.4$ Hz, 1H), 4.40 (dd, $^1J = 6.8$ Hz, $^2J = 1.4$ Hz, 1H), 2.25 (s, 3H).

2.2.1.2. 2,4-Dichlorophenyl vinyl ether. B.p. 104°C at 10 mmHg (lit. 120°C at 21 mmHg [35]); mass spectra: EI (70 eV) *m/z*: 190 $[M + 2]^+$, 188 $[M]^+$, 133, 98, 63. ^{1}H NMR ($CDCl_3$), δ (ppm): 7.47–6.94 (m, 3H, Ar), 6.56 (dd, $^1J = 13.9$ Hz, $^2J = 6.9$ Hz, 1H,), 4.76 (dd, $^1J = 13.9$ Hz, $^2J = 1.8$ Hz, 1H), 4.53 (dd, $^1J = 6.9$ Hz, $^2J = 1.8$ Hz, 1H).

2.3. General procedure for the hydroformylation of aryl vinyl ethers

A 150-ml stainless steel reaction vessel was charged under nitrogen purge with 5 mmol of the substrate, 0.016 mmol of rhodium catalyst, 0.032 mmol of the ligand of choice and 10 ml of anhydrous toluene. The reactor was then pressurized to 80–100 atm with synthesis gas ($CO/H_2 = 1$) and heated at 80–100°C for the due time (see tables). From the reaction mixture the aldehydes were purified by flash chromatography on silica gel using a 9:1 hexane/ethyl acetate mixture as eluent.

The aldehydes obtained, 2-phenoxypropanal, 3-phenoxypropanal, 2-(2-methyl-4-chlorophenoxy)propanal, 3-(2-methyl-4-chlorophenoxy)propanal, 2-(2,4-dichlorophenoxy)propanal, 3-(2,4-dichlorophenoxy)propanal gave ^{1}H NMR patterns consistent with their structures.

2.4. 2-Phenoxypropanal

B.p. 88–90°C at 10 mmHg (lit. 99–101°C at 16 mmHg [37]); mass spectrum: EI (70 eV) *m/z*: 151 $[M + 1]^+$, 150 $[M]^+$, 121, 93, 77. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.64 (d, $J = 1.8$ Hz, 1H) 7.40–6.67 (m, 5H, Ar), 4.52 (q, $J = 5.8$ Hz, 1H), 1.46 (d, $J = 5.8$ Hz, 3H).

2.5. 3-Phenoxypropanal

B.p. 91–93°C at 10 mmHg; mass spectrum: EI (70 eV) *m/z*: 151 $[M + 1]^+$, 150 $[M]^+$, 122, 94, 77. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.74 (t, $J = 1.7$ Hz, 1H) 7.35–6.65 (m, 5H, Ar), 4.18 (t, $J = 4.8$ Hz, 2H), 2.75 (t, $J = 4.8$ Hz, 2H).

2.6. 2-(2-Methyl-4-chlorophenoxy)propanal

B.p. 84–86°C at 0.5 mmHg; mass spectrum: EI (70 eV) *m/z*: 200 $[M + 2]^+$, 198 $[M]^+$, 169, 141, 127, 125. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.60 (d, $J = 1.6$ Hz, 1H) 7.38–6.46 (m, 3H, Ar), 4.51 (q, $J = 8.3$ Hz, 1H), 2.23 (s, 3H), 1.43 (d, $J = 8.3$ Hz, 3H).

2.7. 3-(2-Methyl-4-chlorophenoxy)propanal

B.p. 87–89°C at 0.5 mmHg; mass spectrum: EI (70 eV) *m/z*: 200 $[M + 2]^+$, 198 $[M]^+$, 142, 107, 77. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.78 (t, $J = 1.4$ Hz, 1H) 7.34–6.42 (m, 3H, Ar), 4.18 (t, $J = 6.4$ Hz, 2H), 2.75 (dt, $^1J = 6.4$ Hz, $^2J = 1.4$ Hz, 2H), 2.31 (s, 3H).

2.8. 2-(2,4-Dichlorophenoxy)propanal

M.p. 62–65°C; mass spectrum: EI (70 eV) *m/z*: 220 $[M + 1]^+$, 219 $[M]^+$, 161, 124, 75. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.69 (d, $J = 1.3$ Hz, 1H) 7.40–6.63 (m, 3H, Ar), 4.54 (q, $J = 9.8$ Hz, 1H), 1.45 (d, $J = 9.8$ Hz, 3H).

2.9. 3-(2,4-Dichlorophenoxy)propanal

M.p. 62–64°C; mass spectrum: EI (70 eV) *m/z*: 220 $[M + 1]^+$, 219 $[M]^+$, 189, 162, 125,

109. ^{1}H NMR ($CDCl_3$), δ (ppm): 9.98 (t, J = 1.4 Hz, 1H) 7.42–6.65 (m, 3H, Ar), 4.22 (t, J = 8.5 Hz, 2H), 2.83 (t, J = 8.5 Hz, 2H).

2.10. General procedure for the oxidation of oxo-aldehydes to the corresponding carboxylic acids

The reaction was carried out following the experimental procedure described by Dalcanale and Montanari [38].

To a solution of the oxo-aldehyde (4.7 mmol) in acetonitrile (5.6 ml) and NaH_2PO_4 (152 mg) in H_2O (2.2 ml) and H_2O_2 35% (0.5 ml) was added a solution of $NaClO_2$ (0.72 g, 6.3 mmol) in H_2O (6.3 ml) keeping the temperature at 10°C by water cooling. During the reaction (about 2 h) oxygen was evolved and monitored with a bubbler connected to the apparatus. At the end of the reaction Na_2SO_3 (60 mg) was added to destroy the unreacted HOCl and H_2O_2. The reaction mixture was then acidified with 10% aqueous HCl, extracted with Et_2O and the extracts dried over Na_2SO_4. The acids were obtained in 80–85% yield and were purified by transformation into their sodium salts. All compounds were consistent with reported literature data [39–41].

2.11. Determination of optical purity and enantiomeric excesses of 2-aryloxypropanoic acids

The optical purity of the three chiral 2-aryloxypropanoic acids was determined on the basis of maximum rotatory powers reported in the literature [39–41]. In all cases, these data are compared with enantiomeric excesses determined by enantioselective HPLC. The HPLC analyses were performed using a HPLC chromatograph equipped with UV detector and a Chiracel OD chiral column (25 × 4.6 id), using *n*-hexane/2-propanol/formic acid 90:10:1 as eluent at 0.5 ml/min flow rate. Separation factors α were >1.35. The difference between the values of optical purity and ee are small (2–5%).

2.12. Preparation of diphosphite ligands

2.12.1. Bis(4-methoxyphenyl)-phosphorochloridite

PCl_3 (12.28 g, 7.80 ml, 89.4 mmol) and 4-methoxyphenol (3.0 g, 24.16 mmol) were heated at 65°C overnight under a positive pressure of nitrogen. The excess of PCl_3 was removed under vacuum and the crude solid was used without purification; ^{31}P NMR: δ 159.8.

2.12.2. Bis(2-t-butylphenyl)-phosphorochloridite

This was obtained as a white solid following the above procedure; ^{31}P NMR: δ 161.0.

2.12.3. 1,1′-Binaphthalene-2,2′-dihyl-[tetrakis-4-methoxyphenyloxy]diphosphite (**12**)

To a solution of bis(4-methoxyphenyl)-phosphorochloridite (1.75 g, 5.6 mmol) in benzene (15 ml) a solution of BINOL (0.80 g, 2.8 mmol) and Et_3N (2.26 g, 3.12 ml, 22.4 mmol) in benzene (20 ml) was added dropwise at −40°C. The mixture of reaction was allowed to warm at 0°C for 13 h and then 3 h at room temperature. The turbid mixture was filtered through celite with a fibrous glass frit. The resulting solution of phosphite **12** (1.40 g, 1.68 mmol, 60%) was used for preparation of the catalytic complex without further purification; ^{31}P NMR: δ 145.5.

2.12.4. 1,1′-Binaphthalene-2,2′-dihyl-[tetrakis-2-t-butyl-phenyloxy]diphosphite (**13**)

This was obtained in 65% yield following the above procedure; ^{31}P NMR: δ 146.2.

2.12.5. 4,4′-[[1,1′-Binaphthalene]-2,2′-dihyl-bis-(oxy)]bis-dinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine (**10**)

This was prepared according to the literature procedure [20]:

(a*R*,a*S*,a*R*)-**10** and (a*S*,a*R*,a*S*)-**10**; ^{31}P NMR: δ 145.2;

(a*R*,a*S*,a*S*)-**10** and (a*S*,a*S*,a*R*)-**10**; ^{31}P NMR: δ 144.9 (d, $^7J_{pp'}$ = 16.9 Hz), 146.5 (d, $^7J_{p'p}$ = 16.9 Hz);

(a*R*,a*R*,a*R*)-**10** and (a*S*,a*S*,a*S*)-**10**; ^{31}P NMR: δ 146.0;
(a*R*,a*R*,a*R*)-**10**; ^{31}P NMR: δ 146.0.

*2.12.6. 4,4′-[[1,1′-Binaphthalene]-3,3′-bis(trimethylsilyl)-2,2′-dihyl-bis(oxy)bis-3,3′-bis(trimethyl silyl) - dinaphtho[2,1-d:1′,2′ - f][1,3,2]dioxaphosphepine (**14**)*

This was obtained in 60% yield; (a*R*,a*R*, a*R*)-**14** following the procedure for the preparation of **10**; ^{31}P NMR: δ 130.0.

*2.12.7. 2,4-bis[Dinaphtho[d,f]1,3,2]dioxaphosphepin-6-yloxy]pentane (**11**)*

It was prepared according to the literature procedure [18]:
(a*S*,*R*,*R*,a*R*)-**11** or (a*R*,*R*,*R*,a*S*)-**11**; ^{31}P NMR: δ 148.9 (d, $^{6}J_{pp'} = 9.5$ Hz), 153.8 (d, $^{6}J_{p'p} = 9.5$ Hz);
(a*S*,*R*,*R*,a*S*)-**11**; ^{31}P NMR: δ 146.9;
(a*R*,*R*,*R*,a*R*)-**11**; ^{31}P NMR: δ 153.8.

*2.12.8. 4,8-bis[Dinaphtho[d,f]1,3,2]dioxaphosphepin-6-yloxy] 1,4:3,6-dianhydro-D-mannitol (**15**)*

This was obtained in 65% yield following the procedure for the preparation of **11**;
(a*R*,*R*,*R*,*R*,a*R*)-**15** and (a*S*,*R*,*R*,*R*,a*S*)-**15**; ^{31}P NMR: δ 146.1 one diastereomer, 146.4 one diastereomer;
(a*R*,*R*,*R*,*R*,a*S*)-**15** or (a*S*,*R*,*R*,*R*,a*R*)-**15**; ^{31}P NMR: δ 145.5 (d, $^{7}J_{pp'} = 16.8$ Hz), 147.2 (d, $^{7}J_{p'p} = 16.8$ Hz).

*2.12.9. 2,3-Bis[dinaphtho[d,f]1,3,2]dioxaphosphepin-6-yloxy]pinane (**16**)*

(1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol (107 mg, 0.63 mmol) in anhydrous THF (2 ml) was treated with *n*-BuLi (1 ml of 1.6 M hexane solution, 1.26 mmol). This solution was added dropwise to a solution of bis(1,1′-binaphthalene-2,2′-dihyl)-phosphorochloridite (453 mg, 1.29 mmol) in anhydrous THF (4 ml). The solvent was evaporated under vacuum and anhydrous toluene (10 ml) was added, in order to separate the inorganic salts by filtration under inert atmosphere. After ^{31}P NMR analysis, the solution containing the desired diphosphite **16** was used for the hydroformylation reaction without further purification. (a*R*,1*S*,2*S*,3*R*,5*S*,a*R*)-**16**; ^{31}P NMR: δ 164.6 (d, $^{5}J_{pp'} = 12.3$ Hz); 161.8 (d, $^{5}J_{p'p} = 12.3$ Hz).

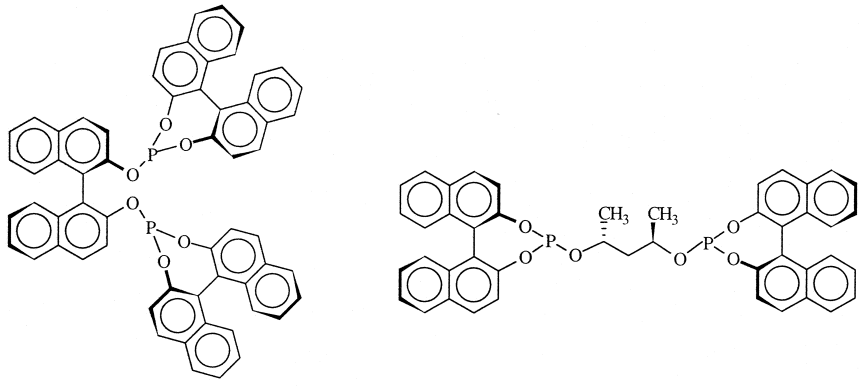
3. Result and discussion

In the aim to prepare active and stereoselective diphosphite ligands for the hydroformylation of aryl vinyl ethers, at first we prepared the known diphosphites **10** [28] and **11** [18] both as mixture of diastereomers and in diastereopure form (Fig. 1).

They were prepared starting from commercial reagents in satisfactory yield (60–70%) and by a well described experimental procedure [18,42] (Scheme 2).

We have used (a*R*)-(+)-1,1′-binaphthalene-2,2′-diol as starting material for the preparation of diastereopure **10** and (a*R*)-(+)-1,1′-binaphthalene-2,2′-diol and (2*R*,4*R*)-pentandiol as starting materials for the preparation of diastereopure **11**, respectively (Scheme 2). Both diastereopure diphosphites (a*R*,a*R*,a*R*)-**10** and (a*R*,*R*,*R*,a*R*)-**11** have a C_2 symmetry axis: as expected, a single signal has been observed in the ^{31}P NMR spectrum of each of them. Six lines are observed for the mixture of diastereomers **10** and **11**, respectively, in the ^{31}P NMR spectrum with chemical shifts consistent with the presence of three diastereomers (two singlets and one double doublet).

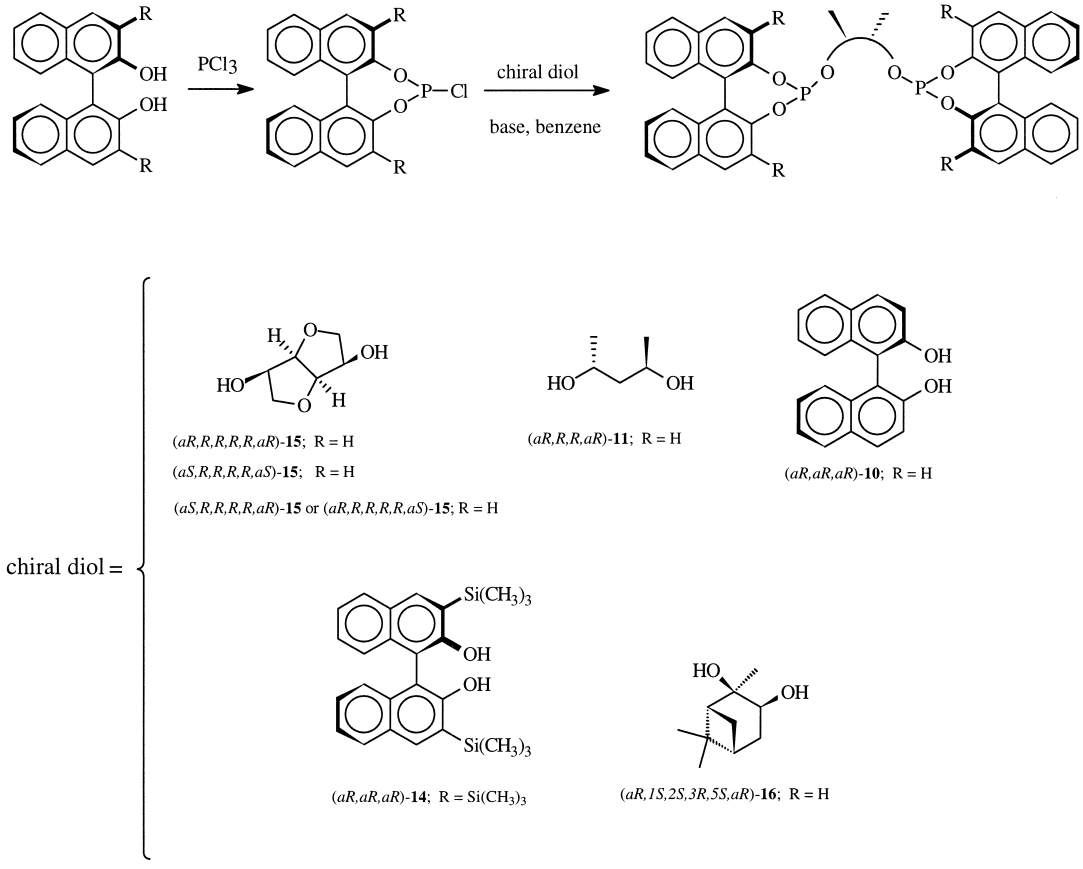
A mixture of diastereomers **10** and **11**, respectively, were used as ligands in the hydroformylation of aryl vinyl ethers **1, 2, 3** (Scheme 1): the reaction was carried out generally in toluene at 80°C and 90 atm. ($CO/H_2 = 1{:}1$), using a catalytic system prepared in situ by mixing $Rh(CO)_2(acac)$ and the appropriate ligand in the same solvent (molar ratio Rh/ligand 1 to 2.0–2.5). According to the literature data [9,10], these catalysts appeared to be very effective also in the hydroformylation of phenyl



(a*R*,a*R*,a*R*)-**10** (a*R*,*R*,*R*,a*R*)-**11**

Fig. 1. Sterically hindered phosphites **10** and **11**.

vinyl ether, giving high yields (80–90%) of the desired branched aldehyde. We have tested, in the same reaction, ligands (a*R*,a*R*,a*R*)-**10** as well as (a*R*,*R*,*R*,a*R*)-**11**: the results are reported in Table 1 (runs 1, 2, and 3). Both diastereomerically pure ligands reproduce very



Scheme 2.

Table 1
Hydroformylation of phenyl vinyl ether using rhodium complexes modified with bulky chiral non-racemic phosphites

Run	Ligand	Rh/ligand	*T*, °C	Reaction time, h	Conv., %	Yield, %	B/L	ee
1	10	1/2	80	15	98	86	87/13	5.8
2	10	1/2.5	30	21	4	3	40/60	1.0
3	11	1/2	80	24	100	80	100	3.0
4	12	1/2	80	22	73	54	88/12	2.1
5	12	1/3	30	40	12	5	50/50	1.3
6	13	1/2.5	80	4	99	86	90/10	2.1
7	14	1/2	80	1.5	100	81	90/10	1.3
8	15	1/2.5	80	4	90	87	80/20	1.6
9	16	1/2	80	22	90	85	75/25	1.0

General hydroformylation conditions: catalytic precursor $Rh(CO)_2(acac)$, substrate/catalyst ratio = 300, CO/H_2 1:1 90 atm.

well the high chemo- and regioselectivity obtained using the corresponding mixture of diastereomers; but, the enantiomeric excesses of the 2-phenoxypropanal (**4**) product were very low for both (a*R*,a*R*,*R*)-**10** and (a*R*,*R*,*R*,a*R*)-**11**. Interestingly, the oxo-reaction carried out at 30°C (Table 1, run 2), which shows a very low reaction rate (4% conversion after 21 h) exhibits opposite regioselectivity. This result might be due to the different coordination mode of the ligand to the metal atom depending on the temperature: it is possible that the chelate complex concentration in the reaction solution is higher in the reaction carried out at 30°C than that carried out at 80°C. This fact should favour the formation of the linear aldehyde.

Owing to negligible enantioselectivities obtained, new chiral phosphite ligands **12, 13, 14, 15**, and **16** were designed and synthesised (Fig. 2).

All of them still possess the binaphthyl moiety, but differ from diphosphites **10** and **11** in electronic and steric contributes.

Ligands **10**, **11**, **14**, and **15** were readily prepared in satisfactory yields (60–65%) from 1,1′-binaphthalene-2,2′-diol and phosphorus(III) chloride in the presence of the appropriate hydroxy derivatives using triethylamine as an acid acceptor. Ligands **12** and **13** were obtained starting from the corresponding phenol via chlorodiphenyl phosphite derivative and further reaction with BINOL (Scheme 3). Ligand **16** was obtained by reaction of the lithium alkoxide derivative of (+)-pinanediol and 1,1′-binaphthalene-2,2′-diol and phosphorus(III) chloride in THF (Scheme 2).

Ligands **12** and **13**, bearing more flexible substituents around both phosphorus atoms, should reduce the steric hindrance around the rhodium atom in the catalytic complex with respect to ligand **10**. Accordingly, we have thought that the catalysts containing diphosphites **12** and **13**, respectively, would promote higher enantioselectivity than those formed with diphosphite **10** [42,43]. Furthermore, the bulky *t*-butyl groups in the ligand **13** should modify the geometry around the phosphorus atom (tetrahedral–pyramidal) [21]; on the other hand, the methoxy group in the *para* position on the phenyl rings of diphosphite **12** should make the phosphorus atoms more electron rich than in the case of the diphosphite **10**.

The results of the hydroformylation experiments are given in Table 1 (runs 4, 5 and 6).

The reaction rate found when using the rhodium complex containing ligand **12** was significantly lower than that observed for the complex containing ligand **10**. This confirmed that an increase in electron density on the coordinating phosphorus atom is not beneficial for the catalytical activity of this type of complexes [44]. No appreciable difference in regioselectivities was found and the enantioselectivity was very low (Table 1, run 4).

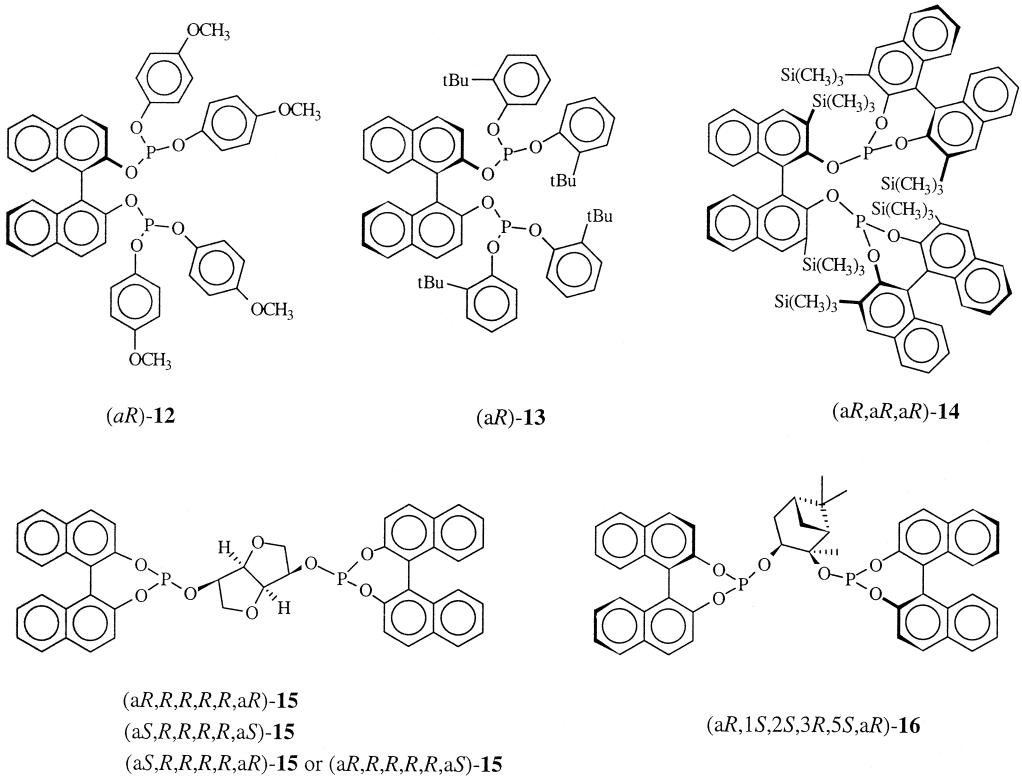
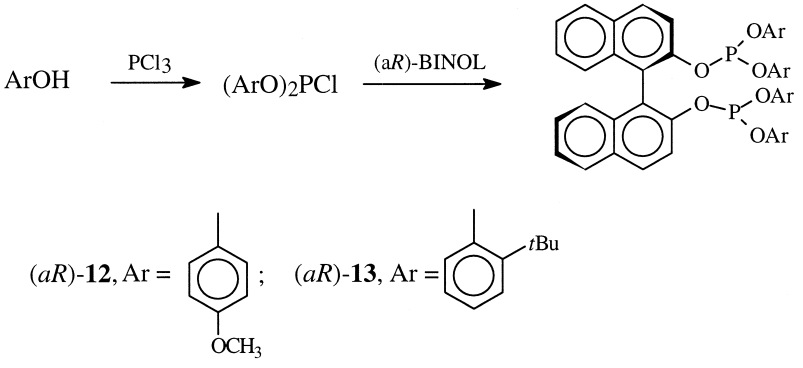


Fig. 2. New chiral diphosphite ligands **12–16**.

When hydroformylation using ligand **12** and **10** was carried out at 30°C, a remarkable decrease in regioselectivity was observed (Table 1, runs 2 and 5).

A very high reaction rate was achieved using rhodium complexes with ligands **13** and **14**, containing bulky substituents in the *ortho* position of phenyl and binaphthyl groups, respectively (Table 1, runs 6 and 7); however, both branched-to-linear aldehyde ratios and asymmetric inductions are affected only to a small extent.

An increase in enantioselectivity was expected for ligand (a*R*,a*R*,a*R*)-**14** with respect



Scheme 3.

to ligand (a*R*,a*R*,a*R*)-**10** according to the results achieved in other enantioselective catalytic processes [45]. The unsuccessful results achieved pointed out that this very sterically hindered ligand may form only a small amount of the most enantioselective chelate complex with rhodium atom.

Diphosphites **11** and **15** contain an alkyl chain bonded to two bulky binaphthyl moieties; they possess chiral centers in the backbone and axial chirality in the terminal groups. This geometry would promote the Rh(I)-complex to get the most enantioselective active complex allowing the binaphthyl arms to lock the final configuration. On the other hand, Rh(I)-complexes of diphosphites **11** and **15** would give matched or mismatched diastereomers and hence a remarkably effect on the selectivity of the hydroformylation would be revealed.

Chiral cooperativity was not observed for ligand (a*R*,*R*,*R*,a*R*)-**11**. This is in agreement with the results reported for the hydroformylation of styrene [18] catalysed by Rh(I) using diastereopure (a*R*,*R*,*R*,a*R*)-**11** as well as (a*S*,*R*,*R*,a*S*)-**11**, although a chiral cooperative effect between stereocentres and stereoaxes in coordinated ligands have been recently demonstrated in catalysis [17,19]. With this aim in mind, the more hindered alkylbinaphthyl phosphite **15** was prepared starting from 1,4:3,6-dianhydro-D-mannitol and racemic BINOL. As a consequence of the binaphthyl configuration, phosphite **15** exists in three possible diastereoisomeric forms (a*R*,*R*,*R*,*R*,*R*,a*R*)-**15**, (a*S*,*R*,*R*,*R*,*R*,a*S*)-**15**, and (a*S*,*R*,*R*,*R*,*R*,a*R*)-**15** (and their enantiomers, respectively), of which only diastereopure (a*R*,*R*,*R*,*R*,*R*,a*R*)-**15** and (a*S*,*R*,*R*,*R*,*R*,a*S*)-**15** possess a C_2 symmetry axis. Unfortunately no chiral cooperativity was observed either for ligand **15** but, in this case, a mixture of diasterermers was used.

In order to study the influence of the stiffness of alkyl-bridge we compared the results obtained with diphosphites **15** with those achieved using diphosphite **16** prepared from commercially available (1*R*,2*R*,3*S*,5*R*)-2,3-pinanediol. However, chemo-, regio- and enantioselectivities are rather similar (Table 1, runs 8 and 9) but they exhibit different reactivity.

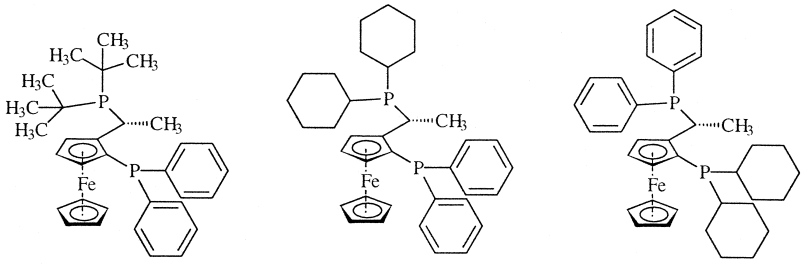
The results obtained in the hydroformylation of 2-methyl-4-chlorophenyl vinyl ether (**2**) and 2,4-dichlorophenyl vinyl ether (**3**) are collected in Table 2.

Only few comments can be made. The reaction rates observed are in all cases satisfactory, reaching generally values $>90\%$ for the sub-

Table 2
Hydroformylation of 2-methyl-4-chlorophenyl vinyl ether and 2,4-dichlorophenyl vinyl ether using rhodium complexes modified with bulky chiral non-racemic phosphites

Run	Substrate	Ligand	Conv., %	Yield, %	B/L	ee, %
1	2-methyl-4-chlorophenyl vinyl ether	10	88	70	99/1	4.3
2	2,4-dichlorophenyl vinyl ether	10	99	83	99/1	3.2
3	2-methyl-4-chlorophenyl vinyl ether	11	99	78	99/1	2.8
4	2,4-dichlorophenyl vinyl ether	11	98	82	99/1	2.1
5	2-methyl-4-chlorophenyl vinyl ether	12	98	92	87/13	2.0
6	2,4-dichlorophenyl vinyl ether	12	90	83	90/10	1.4
7	2-methyl-4-chlorophenyl vinyl ether	13	100	90	92/8	2.0
8	2,4-dichlorophenyl vinyl ether	13	100	87	90/10	1.6
9	2-methyl-4-chlorophenyl vinyl ether	14	100	92	86/14	1.5
10	2,4-dichlorophenyl vinyl ether	14	100	89	91/9	1.1
11	2-methyl-4-chlorophenyl vinyl ether	15	88	80	82/18	1.8
12	2,4-dichlorophenyl vinyl ether	15	82	79	75/25	1.2
13	2-methyl-4-chlorophenyl vinyl ether	16	90	88	70/30	0.8
14	2,4-dichlorophenyl vinyl ether	16	93	86	73/27	0.5

General hydroformylation conditions: catalytic precursor $Rh(CO)_2(acac)$, substrate/catalyst ratio = 300, Rh/ligand ratio = 1:2, CO/H_2 1:1 90 atm, reaction temperature 80°C, reaction time = 24 h.



(a*R,S*)-**17** (a*R,S*)-**18** (a*R,S*)-**19**

Fig. 3. Commercially available chiral non-racemic ferrocenyldiphosphines.

strate conversion at 24 h. Only where methyl and chloro groups are present in the phenyl ring slower rates were observed. All ligands except diphosphite **15** and **16** strongly promote the formation of branched aldehydes (> 85%); the asymmetric inductions, however, are disappointingly low (< 4%).

Ferrocenyldiphosphines present within the wide family of chiral ligands for enantioselective homogeneous catalysis some outstanding features: (i) they can be prepared in enantiomerically pure form through rather accessible and general methods [46]; (ii) they are rather stable compounds; (iii) they promote high chemo- and enantioselectivities in the asymmetric catalysis of several classes of reaction, in particular in hydrogenation and cross-coupling reactions [47]. To our knowledge, no reports are appeared in the literature concerning enantioselective hydroformylation catalyzed by rhodium complexes with ferrocenyldiphosphine ligands. Because of the features above described, we decided to subject aryl vinyl ethers **1**–**3** to the oxo-reaction in the presence of rhodium catalysts in situ formed using commercially available chiral ligands **17**–**19** (Fig. 3).

Working under standard oxo-conditions, reaction rates and aldehyde yields are generally good; however, in some cases the chemoselectivity is strongly lowered by a side reaction which produces phenols.

Up to 29% of 2,4-dichlorophenol was detected, for example, in the reaction mixture, when substrate **3** was hydroformylated in the

Table 3
Hydroformylation of phenyl vinyl ethers using rhodium complexes modified with chiral non-racemic ferrocenylphosphines

Run	Substrate	Reaction time, h	Ligand	Conv., %	Yield, %	B/L	ee, %
1	phenyl vinyl ether	24	17	99.4	93.7[a]	81/9	< 1
2	phenyl vinyl ether	23	18	99.5	92.7[a]	75/25	4.0
3	phenyl vinyl ether	24	19	99.2	95.8[a]	81/9	1.2
4	2-methyl-4-chlorophenyl vinyl ether	24	17	99.3	92.4[a]	87/13	9.2
5	2-methyl-4-chlorophenyl vinyl ether	24	18	99.5	90.1[a]	84/16	2.6
6	2,4-dichlorophenyl vinyl ether	24	17	99.3	61.4[b]	54/46	1.0
7	2,4-dichlorophenyl vinyl ether	24	18	99.4	82.0[c]	78/22	2.4
8	2,4-dichlorophenyl vinyl ether	26	19	99.3	88.6[d]	84/16	5.0

General hydroformylation conditions: catalytic precursor $Rh(CO)_2(acac)$, substrate/catalyst ratio = 500, Rh/ligand ratio = 1:2, CO/H_2 1:1 100 atm., reaction temperature 80°C, reaction time = 24 h.

[a] From 1.4 to 7.8% of the corresponding phenol was present in the reaction mixture.

[b] About 4% of reduction product of the substrate and 29% of 2,4-dichlorophenol was detected in the reaction mixture.

[c] A total of 17% of 2,4-dichlorophenol was present in the reaction mixture.

[d] A total of 10% of 2,4-dichlorophenol was present in the reaction mixture.

presence of the catalyst containing ligand **17** (Table 3, run 6).

In our opinion, the formation of phenols is due to cleavage of aryloxyaldehydes, which is promoted by electron-withdrawing substituents on the aromatic ring. It is not clear how this decomposition is promoted by rhodium complexes with this type of ligands, whereas this side reaction is negligible when rhodium complexes with diphosphite ligands are employed.

In most cases a high proportion of branched aldehyde was found (up to $> 87\%$); the enantioselectivities were again unsatisfactory, not exceeding 10%.

4. Concluding remarks

The hydroformylation of aryl vinyl ethers catalysed by carbonyl rhodium complexes modified with new diphosphites **12–16** at 80°C and 90 atm. ($CO/H_2 = 1$) is an effective method for the preparation of 2-aryloxyaldehydes valuable precursor of important herbicides such as *Mecoprop* and *Dichlorprop*. In most cases high chemo- and regioselectivities towards the formation of the desired branched aldehyde are achieved ($> 80\%$). In particular, ligands **13**, **14**, and **15** promote very high reaction rates: about 90% yield of 2-phenoxyaldehydes are obtained in 1.5–4 h under standard oxo-conditions.

The presence of methyl and chloro substituents on the aromatic ring, seems to have some influence on the reaction rate, but does not change appreciably the chemo- and regioselectivity of the hydroformylation.

Rhodium complexes with ferrocenyldiphosphines are inferior catalysts with respect to those formed with diphosphites: in particular, the chemoselectivity is lowered by a side reaction which transforms the phenoxy groups into the corresponding phenols under oxo-conditions.

The enantioselectivities in all cases are unsatisfactory ($\leq 10\%$). No chiral cooperative effect between stereocenters and stereoaxes in coordinate diphosphite ligands **11**, **15** and **16** was observed. The low enantioselectivities obtained might be imputed to the presence in the reaction solution of significant amount of non-chelating diphosphite/Rh(I) complexes; however, the fact that the racemization under oxo-conditions of the aryloxyaldehydes may contribute in lowering obtained enantioselectivities cannot be excluded.

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