# Asymmetric hydrogenation of diethyl 1-phenylvinylphosphonate by metal complexes in $CH_2Cl_2$ and in supercritical carbon dioxide using phosphite-type ligands

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Asymmetric hydrogenation of diethyl 1-phenylvinylphosphonate was carried out for the first time in dichloromethane and supercritical carbon dioxide in the presence of phosphite and amidophosphite ligands. The catalysts based on $[Ir(COD)_2]BARF$ (COD is 1,5-cyclooctadiene, BARF is tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion), provide higher enantioselectivity than $[Ir(COD)Cl]_2$ and $[Rh(COD)_2]BF_4$ do.

**Key words:** supercritical carbon dioxide, asymmetric hydrogenation, iridium complexes, phosphonates, amidophosphites.

Phosphonates form an important class of organophosphorus compounds known for their biological activities.[1] In particular, many 1-aryl ethylphosphonates are used as components of anti-inflammatory drugs[2] and for treatment of violations of calcium metabolism in the human organism.[3] However, these compounds are applied presently as racemic mixtures, which is significantly less efficient than the use of enantiomerically pure compounds. Moreover, an enantiomer without a desired biological activity can exert a negative effect on the health of a patient.[4] A promising method for the synthesis of these phosphonates is the steroselective hydrogenation of prochiral unsaturated phosphonates by metal complexes. In this process, the iridium, rhodium, and ruthenium catalysts with phosphine ligands were approved,[5—8] but their preparation is a fairly complicated procedure that requires an improved technique of operations with such sensitive reagents as butyllithium. It was shown rather recently that easily accessible phosphite and amidophosphite ligands can compete with phosphine systems in asymmetric hydrogenation of unsaturated substrates.[9] In spite of this, there are no published examples for the use of ligands of the phosphite type in the hydrogenation of prochiral unsaturated phosphonates. The application of chiral phosphites and amidophosphites makes it possible to attain high conversions and enantioselectivities in both organic solvents and alternative reaction media.[10—13] One of the most promising media is supercritical carbon dioxide ($scCO_2$), which is readily accessible and has a high self-diffusion coefficient and, hence, is easily miscible with reaction gases. In addition, the use of $CO_2$ does not violate fire and ecological safety.[14] In this work, we pioneered in using phosphite and amidophosphite ligands in the Rh- and Ir-catalyzed hydrogenation of diethyl 1-phenylvinylphosphonate in dichloromethane and in supercritical carbon dioxide.

## Results and Discussion

The primary experiments on the hydrogenation of diethyl 1-phenylvinylphosphonate (**1**) were carried out in dichloromethane, which is an optimum solvent for the Rh-catalyzed hydrogenation of unsaturated substrates involving ligands of the phosphite type.[15—17] The systems consisting of the rhodium precursor $[Rh(COD)_2]BF_4$ (COD is 1,5-cyclooctadiene) and known ligands **L1**, **L2**, and **L3** (Scheme 1, Table 1) were chosen as catalysts.

The complete conversion of the substrate occurred within 8 h under an enhanced hydrogen pressure (50 atm) and at a catalyst to substrate mole ratio of 1 : 100 (L/Rh = 2 : 1) in the presence of all ligands. However, the reaction products were obtained as racemic mixtures. For the purpose of optimizing the process, we replaced the rhodium metal complex precursor by the iridium one: $[Ir(COD)Cl]_2$. For the catalytic systems based on $[Ir(COD)Cl]_2$ and ligands **L1**—**L3**, the conversion decreased (13—51%) but enantioselectivity appeared (see Table 1, entries *4—6*).

Among these ligands amidophosphite ligand **L1** showed the highest conversion and enantioselectivity, whereas phosphite ligand **L2**, and phosphite **L3** with the trifluoroethyl substituent are characterized by the lowest conversion and enantioselectivity. We also used the iridium precursor containing a weakly coordinated tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion (BARF): $[Ir(COD)_2]$-

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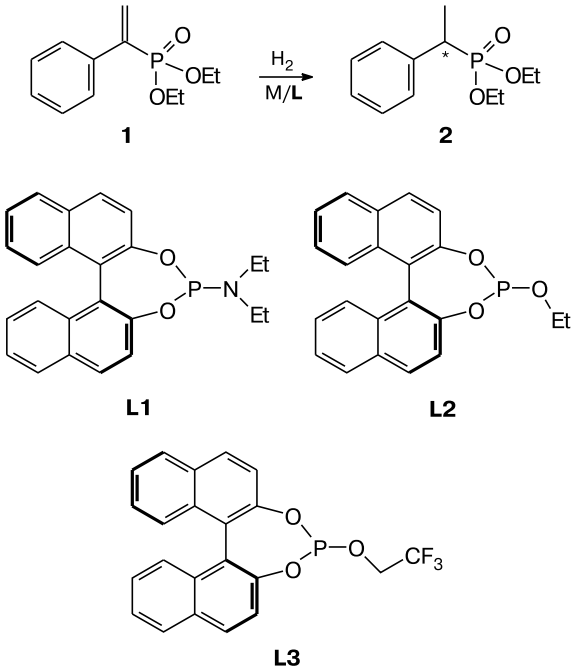
**Scheme 1**




BARF.[18] According to published data, the catalytic system $[Ir(COD)_2]BARF/2\mathbf{L}$ based on amidophosphite ligands makes it possible to carry out the asymmetric hydrogenation of various prochiral imines, which are fairly inert substrates, with high conversion and enantioselectivity (up to 99% *ee*).[19] Indeed, in our case, the use of the $[Ir(COD)_2]BARF/2\mathbf{L}$ system in $CH_2Cl_2$ significantly increased the enantiomeric excess (see Table 1, entries *7—9*) compared to $[Ir(COD)Cl]_2$. The reaction conducted in $scCO_2$ as a reaction medium, which possesses unique physicochemical properties,[14] in the presence of the catalysts obtained in dichloromethane followed by solvent removal *in vacuo* proceeded with an increased rate, and enantioselectivity was also enhanced in several cases. For example, in the case of amidophosphite **L1** at 25 atm of $H_2$ (total pressure 120 atm) and 60 °C, the maximum conversion within 8 h was 68% and enantioselectivity was 51% (see Table 1, entry *10*). The use of phosphite ligands **L2** and **L3** considerably decreases enantioselectivity and conversion (see Table 1, entries *11* and *12*). With an increase in the total pressure to 200 atm, higher conversion and enantioselectivity were also observed when using amidophosphite ligand **L1** (see Table 1, entries *13—15*). At the same time, the conversion and enantioselectivity are lower in the presence of phosphite **L2**, whereas ligand **L3** results in the racemic product with the lowest conversion. The conversion values turned out to be similar for all ligands with an increase in the total pressure from 200 to 250 atm (hydrogen pressure 25 atm); however, a higher enantioselectivity was obtained for amidophosphite **L1** (see Table 1, entries *16—18*). For the enhanced (to 50 atm) hydrogen pressure, the highest enantioselectivity (*ee* 62%) is also observed in the case of ligand **L1** compared to phosphites **L2** and **L3** (see Table 1, entries *19—21*).

**Table 1.** Results of hydrogenation of diethyl 1-phenylvinylphosphonate[a]

| Entry | Catalyst M/**L** | Medium ($P_{tot}$/atm) | $P_{H_2}$ /atm | $C^b$ (%) | *ee* (%) |
|---|---|---|---|---|---|
| *1* | $[Rh(COD)_2]BF_4/2\mathbf{L1}$ | $CH_2Cl_2$ | 50 | 100 | 0 |
| *2* | $[Rh(COD)_2]BF_4/2\mathbf{L2}$ | $CH_2Cl_2$ | 50 | 100 | 0 |
| *3* | $[Rh(COD)_2]BF_4/2\mathbf{L3}$ | $CH_2Cl_2$ | 50 | 100 | 0 |
| *4* | $[Ir(COD)Cl]_2/2\mathbf{L1}$ | $CH_2Cl_2$ | 50 | 51 | 39(*S*) |
| *5* | $[Ir(COD)Cl]_2/2\mathbf{L2}$ | $CH_2Cl_2$ | 50 | 30 | 7(*S*) |
| *6* | $[Ir(COD)Cl]_2/2\mathbf{L3}$ | $CH_2Cl_2$ | 50 | 13 | 5(*S*) |
| *7* | $[Ir(COD)_2]BARF/2\mathbf{L1}$ | $CH_2Cl_2$ | 50 | 44 | 54(*S*) |
| *8* | $[Ir(COD)_2]BARF/2\mathbf{L2}$ | $CH_2Cl_2$ | 50 | 21 | 33(*S*) |
| *9* | $[Ir(COD)_2]BARF/2\mathbf{L3}$ | $CH_2Cl_2$ | 50 | 15 | 6(*S*) |
| *10* | $[Ir(COD)_2]BARF/2\mathbf{L1}$ | $scCO_2$ (120) | 25 | 68 | 51(*S*) |
| *11* | $[Ir(COD)_2]BARF/2\mathbf{L2}$ | $scCO_2$ (120) | 25 | 19 | 5(*S*) |
| *12* | $[Ir(COD)_2]BARF/2\mathbf{L3}$ | $scCO_2$ (120) | 25 | 51 | 0 |
| *13* | $[Ir(COD)_2]BARF/2\mathbf{L1}$ | $scCO_2$ (200) | 25 | 38 | 60(*S*) |
| *14* | $[Ir(COD)_2]BARF/2\mathbf{L2}$ | $scCO_2$ (200) | 25 | 33 | 7(*S*) |
| *15* | $[Ir(COD)_2]BARF/2\mathbf{L3}$ | $scCO_2$ (200) | 25 | 19 | 0 |
| *16* | $[Ir(COD)_2]BARF/2\mathbf{L1}$ | $scCO_2$ (250) | 25 | 39 | 48(*S*) |
| *17* | $[Ir(COD)_2]BARF/2\mathbf{L2}$ | $scCO_2$ (250) | 25 | 37 | 3(*S*) |
| *18* | $[Ir(COD)_2]BARF/2\mathbf{L3}$ | $scCO_2$ (250) | 25 | 35 | 5(*S*) |
| *19* | $[Ir(COD)_2]BARF/2\mathbf{L1}$ | $scCO_2$ (250) | 50 | 38 | 62(*S*) |
| *20* | $[Ir(COD)_2]BARF/2\mathbf{L2}$ | $scCO_2$ (250) | 50 | 30 | 13(*S*) |
| *21* | $[Ir(COD)_2]BARF/2\mathbf{L3}$ | $scCO_2$ (250) | 50 | 29 | 0 |

[a] The conversion time is 8 h.
[b] Conversion.

Thus, we pioneered in hydrogenating unsaturated phosphonates in dichloromethane and in a medium of supercritical $CO_2$ using the phosphite and amidophosphite ligands. The catalysts based on $[Rh(COD)_2]BF_4$ lead to a racemic product, whereas the use of $[Ir(COD)_2]BARF$ makes it possible to attain higher enantioselectivities than those of $[Ir(COD)Cl]_2$. Higher conversions and enantioselectivities of the product are observed in reactions with both dichloromethane and $scCO_2$ in the presence of amidophosphite ligand **L1** than those obtained with phosphite ligands **L2** and **L3**.

## Experimental

$^{31}P$ and $^1H$ NMR spectra were recorded on a Bruker Avance 400 instrument (161.98 and 400.13 MHz) relative to 85% $H_3PO_4$

in $D_2O$ and $SiMe_4$, respectively. Hydrogenation was carried out in a system from the High pressure equipment Co. equipped with a 10-mL stainless steel autoclave. Optical yields were determined by HPLC on an Agilent HP-1100 chromatograph using the Chiralpac AD column (UV detector, 219 nm, hexane—isopropanol (99 : 1), 1 mL $min^{-1}$).[7] The retention times for enantiomers of diethyl 1-phenylethylphosphonate (**2**) were 16.2 (*S*) and 20.5 (*R*) min, and that for diethyl 1-phenylvinylphosphonate (**1**) was 18.2 min. The conversion of compound **1** was determined using $^1H$ NMR spectroscopy.[5] ($S_a$)-2-(Diethylamino)-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**L1**),[20] ($S_a$)-2-(ethyloxy)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**L2**),[21] ($S_a$)-2-(2,2,2-trifluoroethyloxy)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]-dioxaphosphepine (**L3**),[22] $[Rh(COD)_2]BF_4$,[23] $[Ir(COD)Cl]_2$,[24] and $[Ir(COD)_2]BARF$[25] were synthesized according to published procedures.

**Synthesis of diethyl 1-phenylvinylphosphonate (1).** Diethyl 1-phenylvinylphosphonate (**1**) was synthesized according to a procedure scaled and slightly modified in our group.[26] Benzaldehyde (10 g, 0.094 mol) and nitromethane (5.73 g, 0.094 mol) were added to hydroxyethylammonium acetate[27] (30 g) washed with hexane and dried *in vacuo* (1 Torr). The mixture was stirred for 15 min, and triethyl phosphite (15.62 g, 0.094 mol) was poured to the mixture, which was stirred for 1 h at 5 °C and kept for 24 h at room temperature with reflux condenser. The product was extracted with ethyl acetate (3×25 mL) and purified using flash chromatography on silica gel, the solvent was evaporated, and the product was distilled *in vacuo* to obtain a lightly yellowish oil (b.p. 160 °C, 1.5 Torr). The yield was 7.9 g (35%). The spectral characteristics of compound **1** correspond to literature data.[26] The yield did not exceed 3—5% when using the unmodified procedure[26] with a load of 0.094 mole.

**Asymmetric hydrogenation of diethyl 1-phenylvinylphosphonate (1) in $CH_2Cl_2$ (general procedure).** $[Ir(COD)_2]BARF$ or $[Rh(COD)_2]BF_4$ (0.003 mmol) was dissolved in $CH_2Cl_2$ (2 mL), the corresponding ligand **L1—L3** (0.006 mmol) was added, and the solution was stirred for 5 min. In the case of dimeric $[Ir(COD)Cl]_2$, the weighed sample was 1 mg and contained 0.0015 mmole of the precursor of this metal complex and 0.006 mmole of the ligand. Diethyl 1-phenylvinylphosphonate (**1**) (72 mg, 0.3 mmol) was added to the obtained catalysts, the autoclave was filled with hydrogen (50 atm) and heated to 60 °C (10 min), and the mixture was magnetically stirred. After hydrogen was released, the reaction mixture was diluted with $CH_2Cl_2$ (2 mL) and purified from the catalyst through a thin layer of silica gel, and the solvents were removed *in vacuo*.

**Asymmetric hydrogenation of diethyl 1-phenylvinylphosphonate (1) in a medium of supercritical $CO_2$ (general procedure).** Phosphonate **1** (72 mg, 0.3 mmol) was added to the catalysts prepared (see above) in 0.2 mL of $CH_2Cl_2$ from $[Ir(COD)_2]BARF$ (0.003 mmol) and the corresponding ligand **L1—L3** (0.006 mmol) after the solvent was removed *in vacuo*. The closed autoclave was first filled with hydrogen to a required pressure and then with carbon dioxide. The reactor was heated to 60 °C (10 min), and hydrogenation was carried out with magnetic stirring. After the end of the reaction, $CO_2$ and $H_2$ were slowly released, the reaction mixture was diluted with $CH_2Cl_2$ (2 mL) and purified from the catalyst through a thin layer of silica gel, and the solvent was removed *in vacuo*.

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