Asymmetric hydrogenation with the use of chiral carborane amidophosphite derivatives in supercritical carbon dioxide and CH_2Cl_2

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New chiral carborane-containing amidophosphites containing the BINOL fragment (BINOL stands for 2,2´-dihydroxy-1,1´-binaphthyl) have been synthesized. The study of efficiency of these compounds as ligands in the Rh-catalyzed asymmetric hydrogenation of enamides in supercritical carbon dioxide ($scCO_2$) and CH_2Cl_2 showed that enantioselectivity of the process is considerably higher in $scCO_2$.

Key words: carboranes, asymmetric hydrogenation, amidophosphites, supercritical carbon dioxide, rhodium complexes.

At present, significant amount of chemical reactions is carried out in organic solvents, such as chlorinated hydrocarbons, methanol, acetone, which are significantly dangerous for the environment, that stimulates a search for the alternative, environmentally friendly media. Supercritical carbon dioxide ($scCO_2$) is one of such media because of availability of this compound and its environmental and fire safety.[1,2] In addition, carbon dioxide can be easily and completely removed from the reaction products within several minutes. Despite of this advantages, as of this moment $scCO_2$ is mainly used for extraction[3] and considerably less frequently as the medium for organic synthesis.[1] Note that $scCO_2$ possesses excellent miscibility with gases, for example, with hydrogen, that makes it easy to transport H_2 to the reaction surface of catalysts.[4] In addition, in the case of $scCO_2$ no separation of gaseous and liquid organic phases occurs, that is observed when organic solvents are used in hydrogenation processes. Therefore, the study of hydrogenation in $scCO_2$ is an actual problem. At present, low attention is paid to the asymmetric metal-complex hydrogenation in $scCO_2$, though promising results have been obtained in this field. For instance, the use of metal-complex catalysts with chiral phosphine ligands demonstrated high enantioselectivity in hydrogenation of a series of prochiral unsaturated substrates. Usually, 12—48 h are required to reach the full conversion, that is comparable with the results obtained in organic solvents.[5,6] Earlier,[7—9] it has been shown that chiral phosphites and amidophosphites are more promising ligands for asymmetric hydrogenation in $scCO_2$, which provide the high rate and enantioselectivity of the reaction. One of the new trends in the development of efficient chiral catalysts for hydrogenation processes in $scCO_2$ is incorporation of a bulky carborane group into the ligand composition.[10—12] In the present work, we demonstrate results of testing of new amidophosphite ligands containing carborane substituents in the asymmetric Rh-catalyzed hydrogenation reaction of enamides in $scCO_2$ and CH_2Cl_2 to yield amino acid derivatives.

Results and Discussion

The reaction of *ortho*-carboranylmethyl triflate (**1**) with 4-fluoroaniline (**2**) or cyclopropylamine (**3**) led to carborane-containing amines **4** and **5** (Scheme 1).

Phosphorylation of amines **4** and **5** afforded new chiral carboranyl amidophosphites L^1 and L^2 (Scheme 2).

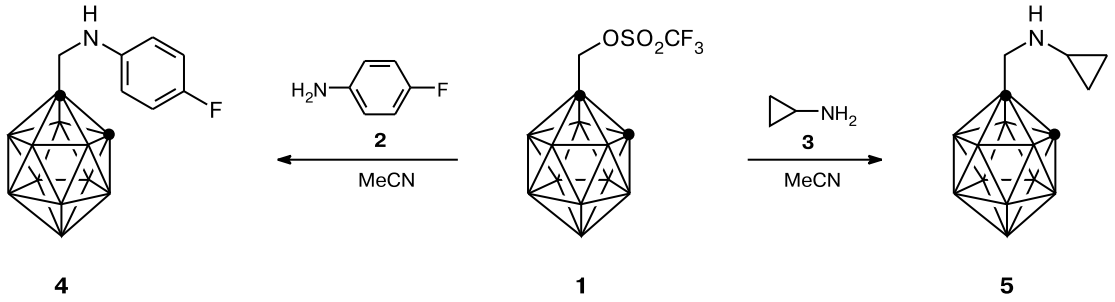
Ligands L^1 and L^2 are well soluble in organic solvents, such as CH_2Cl_2 and C_6H_6. The presence of the fluorine atom in ligand L^1 provides its good solubility also in the nonpolar hexane. Fluorine-containing ligands, as compared to their analogs containing no fluorine atoms, are characterized by better solubility in $scCO_2$ as well, which is a nonpolar enough medium.[5]

Amidophosphites L^1 and L^2 were tested in the Rh-catalyzed asymmetric hydrogenation of a series of enamides **7a—c** — precursors of phenylalanine and its chlorine- and fluorine-containing analogs (Scheme 3, Table 1). Note that *N*-acetyl derivatives of 4-chlorophenylalanine possess antiinflammatory properties, whereas the drugs based on 4-fluorophenylalanine exhibit antimicrobal properties.[9]

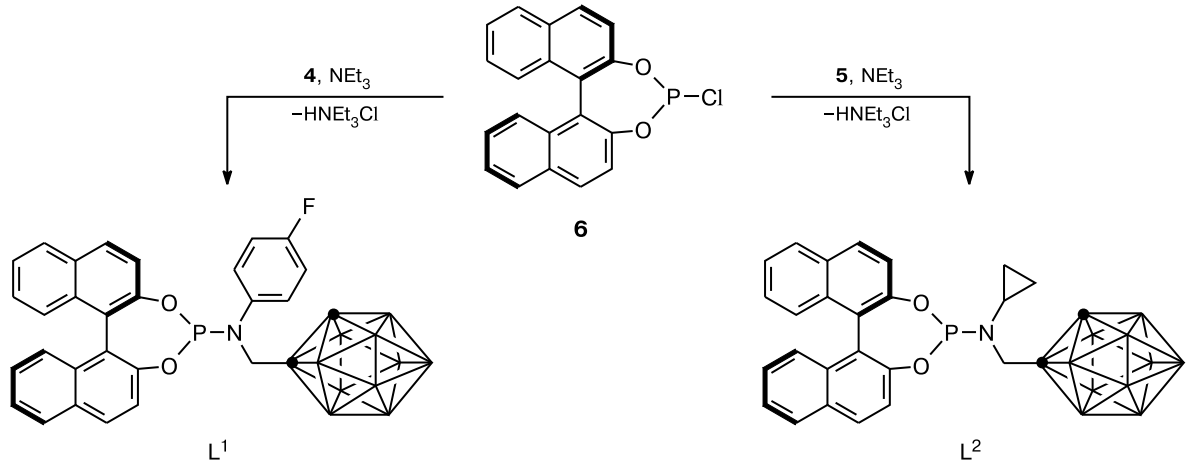
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1787—1790, September, 2010.

1066-5285/10/5909-1836

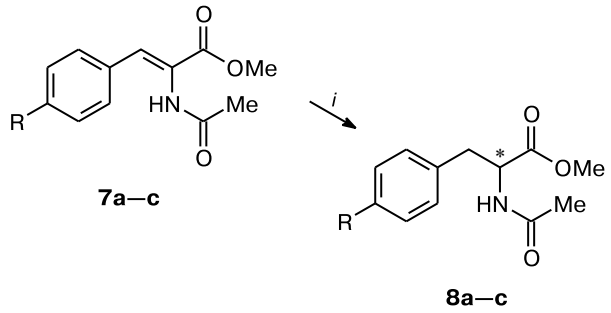
Scheme 1



Scheme 2



Scheme 3



i. H_2, $scCO_2$ or CH_2Cl_2, $[Rh(COD)_2]BF_4$/2L, 0.5 mol.%
R = H (**a**), F (**b**), Cl (**c**)

When the catalyst formed *in situ* starting from ligand L^1 and $[Rh(COD)_2]BF_4$ (COD stands for cyclooct-1,5-diene) was used in $scCO_2$ at high (45 atm) hydrogen pressure and molar ratio of the substrate to the catalyst 200/1, the complete conversion of substrate **7a** was reached in 2 h, and the product had 48% *ee* (see Table 1, entry *1*). A decrease in the pressure of H_2 from 40 to 15 atm allowed us to somewhat increase the enantioselectivity (*cf.* entries *1* and *2*). Application of the same catalytic system $[Rh(COD)_2]BF_4/2L^1$ in CH_2Cl_2 provided only 20% *ee*, with the enantioselectivity remaining the same at both 15 and 40 atm of H_2 (see Table 1, entries *3* and *4*). When amidophosphite L^2 was used in hydrogenation of **7a** at 15 atm of H_2 in $scCO_2$ and CH_2Cl_2 at 45 °C, the $scCO_2$ also provided higher enantioselectivity (see Table 1, entries *5* and *6*). In the hydrogenation of fluorine-containing substrate **7b** using the catalyst based on ligand L^1 in $scCO_2$, 48% *ee* at 40 atm of H_2 and 52% *ee* at 15 atm of H_2 were achieved (see Table 1, entries *7* and *8*). In CH_2Cl_2, 21% *ee* at both high and low pressure of H_2 was observed (entries *9* and *10*). Ligand L^2 in hydrogenation of **7b** provides lower enantioselectivity in both $scCO_2$ and CH_2Cl_2, with the enantiomeric excess of the reaction product **8b** in $scCO_2$ being higher (see Table 1, entries *11* and *12*). Hydrogenation of chlorine-containing enamide **7c** with the use of ligand L^1 gave analogous results. For instance, application of $scCO_2$ provides higher enantioselectivity as compared to CH_2Cl_2 (see Table 1, entries *13*—*16*). Hydrogenation of **7c** using the catalytic system based on amidophosphite L^2 in $scCO_2$ showed that higher pressure of H_2 assists in the increase in conversion (entries *17*—*18*).

Table 1. Hydrogenation of enamides **7a—c** catalyzed by $[Rh(COD)_2]BF_4$/2L (45 °C)

Entry	L	R	P_{H_2} /atm	Medium	*t*/h	P_{tot} /atm	γ^a (%)	ee^b (%)
1	L^1	H	40	$scCO_2$	2	250	100	48
2	L^1	H	15	$scCO_2$	2	250	100	52
3	L^1	H	40	CH_2Cl_2	2	—	100	20
4	L^1	H	15	CH_2Cl_2	2	—	100	20
5	L^2	H	15	$scCO_2$	2	250	100	37
6	L^2	H	15	CH_2Cl_2	2	—	100	22
7	L^1	F	40	$scCO_2$	2	250	100	48
8	L^1	F	15	$scCO_2$	2	250	100	52
9	L^1	F	40	CH_2Cl_2	2	—	100	21
10	L^1	F	15	CH_2Cl_2	2	—	100	21
11	L^2	F	15	$scCO_2$	2	250	100	42
12	L^2	F	15	CH_2Cl_2	2	—	100	30
13	L^1	Cl	40	$scCO_2$	2	250	100	48
14	L^1	Cl	15	$scCO_2$	2	250	100	51
15	L^1	Cl	40	CH_2Cl_2	2	—	100	21
16	L^1	Cl	15	CH_2Cl_2	2	—	100	21
17	L^2	Cl	40	$scCO_2$	3	250	35	36
18	L^2	Cl	15	$scCO_2$	3	250	8	36
19	L^2	Cl	40	CH_2Cl_2	3	—	100	32
20	L^2	Cl	15	CH_2Cl_2	3	—	100	32

[a] γ is the conversion.
[b] *S*-Configuration of products in all the cases.

The full conversion was successfully reached within 3 h in CH_2Cl_2, however, the enantioselectivity has proved somewhat lower than in $scCO_2$ (entries *19—20*).

In conclusion, the asymmetric Rh-catalyzed hydrogenation of enamides involving new carborane-containing chiral amidophosphites in $scCO_2$ and CH_2Cl_2 allows one to reach high conversions at low loading a Rh-catalyst within 2—3 h, with the *ee* values of the products being higher in $scCO_2$.

Experimental

^{31}P, ^1H, and ^{11}B NMR spectra were recorded on an Avance 400 spectrometer (161.98, 400.13, and 128.4 MHz) relatively to 85% H_3PO_4 in D_2O, Me_4Si, and $BF_3 \cdot OEt_2$, respectively. Elemental analysis was performed in the Laboratory of Organic Microanalysis of the A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

All the reactions concerning preparation of catalysts were performed in the atmosphere of dry argon in anhydrous solvents. *o*-Carboranylmethyl triflate (**1**),[13] (R_a)-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (**6**),[14] $[Rh(COD)_2]BF_4$,[15] methyl (*Z*)-2-acetamido-3-phenylacrylate (**7a**),[16] methyl (*Z*)-2-acetamido-3-(4-chlorophenyl)acrylate (**7b**),[16] and methyl (*Z*)-2-acetamido-3-(4-fluorophenyl)acrylate (**7c**)[9] were obtained according to the known procedures.

Synthesis of amines 4 and 5 (general procedure). A mixture of *o*-carboranylmethyl triflate **1** (1.9 g, 6.2 mmol), the corresponding amine (6.5 mmol), NaOAc (0.74 g, 9 mmol) and MeCN (10 mL) was refluxed for 4—8 h (TLC monitoring of conversion of **1** using heptane—EtOAc (7 : 3) as an eluent). Water (20 mL) was added to the reaction mixture, followed by extraction with EtOAc (3×7 mL). A combined organic phase was washed with water, dried with Na_2SO_4, and filtered, the solvent was evaporated *in vacuo*. The products were purified by column chromatography on silica gel (heptane—EtOAc (10 : 1) in the case of **4** and heptane in the case of **5**).

***N*-(*o*-Carboranylmethyl)-*N*-(4-fluorophenyl)amine (4)**, white powder. The yield was 1.07 g (65%), m.p. 82—83 °C. Found (%): C, 40.56; H, 6.88; N, 5.16. $C_9H_{18}B_{10}FN$. Calculated (%): C, 40.43; H, 6.79; N, 5.24. ^1H NMR ($CDCl_3$), δ: 1.38—3.17 (m, 10 H); 3.76 (s, 1 H); 3.86 (s, 2 H); 3.92 (s, 1 H); 6.50—6.60 (m, 2 H); 6.90 (t, 2 H, J = 8.4 Hz). ^{11}B {H} NMR ($CDCl_3$), δ: −14.00÷−10.82 (m, 4 B); −11.52 (s, 2 B); −9.06 (s, 2 B); −5.14 (s, 1 B); −2.31 (s, 1 B). IR ($CHCl_3$): νNH 3440 cm^{-1}.

***N*-(*o*-Carboranylmethyl)-*N*-cyclopropylamine (5)**, viscous colorless oil. The yield was 0.66 g (50%). Found (%): C, 33.84; H, 8.94; N, 6.51. $C_6H_{19}B_{10}N$. Calculated (%): C, 33.78; H, 8.98; N, 6.57. ^1H NMR ($CDCl_3$), δ: 0.24—0.31 (m, 2 H); 0.41—0.49 (m, 2 H); 1.28—3.00 (m, 10 H); 2.14—2.21 (m, 1 H); 3.35 (s, 2 H); 3.94 (s, 1 H). ^{11}B {H} NMR ($CDCl_3$), δ: −14.32÷−14.30 (m, 4 B); −11.41 (s, 2 B); −9.12 (s, 2 B); −5.55 (s, 1 B); −3.11 (s, 1 B). IR ($CHCl_3$): νNH 3336 cm^{-1}.

Synthesis of ligands L^1 and L^2 (general procedure). Triethylamine (0.14 mL, 1.0 mmol) and the corresponding carborane amine **4** or **5** (1.0 mmol) were added to a solution of (R_{ax})-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane[14] (**6**) (0.35 g, 1.0 mmol) in C_6H_6 (15 mL) and the mixture was stirred for 10 min at 20 °C, heated to the reflux, cooled to room temperatures, a precipitate of $HNEt_3Cl$ was filtered off. The products were purified by column flash-chromatography on silica gel (benzene).

(R_{ax})-2-[*N*-(*o*-Carboranylmethyl)-*N*-(4-fluorophenyl)amino]-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (L^1), viscous colorless oil. The yield was 0.49 g (85%). Found (%): C, 59.95; H, 5.12; N, 2.50. $C_{29}H_{29}B_{10}FNO_2P$. Calculated (%): C, 59.89; H, 5.03; N, 2.41. ^{31}P NMR ($CDCl_3$), δ: 136.61. ^1H NMR ($CDCl_3$), δ: 1.36—3.18 (m, 10 H); 3.75 (s, 1 H); 3.84 (s, 2 H); 6.49—6.58 (m, 2 H); 6.90 (t, 2 H, J = 8.6 Hz); 7.21—8.00 (m, 12 H). ^{11}B {H} NMR ($CDCl_3$), δ: −14.18÷−12.16 (m, 4 B); −11.51 (s, 2 B); −9.06 (s, 2 B); −5.15 (s, 1 B); −2.32 (s, 1 B).

(R_{ax})-2-[*N*-(*o*-Carboranylmethyl)-*N*-cyclopropylamino]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (L^2), viscous colorless oil. The yield was 0.42 g (80%). Found (%): C, 59.25; H, 5.80; N, 2.59. $C_{26}H_{30}NB_{10}O_2P$. Calculated (%): C, 59.19; H, 5.73; N, 2.65. ^{31}P NMR ($CDCl_3$), δ: 136.66. ^1H NMR ($CDCl_3$), δ: 0.24—0.32 (m, 2 H); 0.41—0.49 (m, 2 H); 1.20—3.08 (m, 10 H); 2.14—2.21 (m, 1 H); 3.35 (s, 2 H); 3.95 (s, 1 H), 7.20—8.00 (m, 12 H). ^{11}B {H} NMR ($CDCl_3$), δ: −14.32÷−12.21 (m, 4 B); −11.40 (s, 2 B); −9.12 (s, 2 B); −5.52 (s, 1 B); −3.08 (s, 1 B).

Asymmetric hydrogenation of enamides in $scCO_2$ and CH_2Cl_2. The compound $[Rh(COD)_2]BF_4$ (2 mg, 0.005 mmol), the ligand (0.01 mmol), and CH_2Cl_2 (0.3 mL) were placed in a 10-mL autoclave. The mixture was stirred for 2 min, the solvent was evaporated *in vacuo*, followed by addition of the corresponding enamide (**7a—c**) (1 mmol) and CH_2Cl_2 (4 mL), if the latter was used as the solvent. The sealed autoclave was purged with CO_2, filled with hydrogen to the required pressure (see Table 1), then carbon dioxide was added using a High Pressure Equipment to 250 atm. The reactor was heated to the corresponding tempera-

ture (45 °C) for 5 min and the process was performed with stirring using a magnetic stirrer. After the reaction was completed, CO_2 and H_2 were slowly released, conversion was monitored by ^{1}H NMR spectroscopy. Enantiomeric ratio of products **8a—c** was determined by HPLC on an Agilent HP-1100 chromatograph using a Kromasil 5-AmyCoat column according to the procedure given in the literature.[9]

This work was financially supported by the Russian Foundation for Basic Research (Project Nos 09-03-12104-ofi_m and 09-03-91345-NNIO_a).

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Received July 14, 2010