Synthesis of new chiral amidophosphite ligands and their application in hydrogenation of benzodiazepinones and enamides

M. V. Sokolovskaya, S. E. Lyubimov, and V. A. Davankov*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 6471. E-mail: lssp452@mail.ru

New chiral amidophosphites were synthesized and tested in the Ir-catalyzed hydrogenation of 4-substituted 1,3-dihydro-2*H*-1,5-benzodiazepin-2-ones and Rh-catalyzed hydrogenation of dehydro amino acid derivatives. The triphenylphosphine additive can considerably increase the enantioselectivity of both processes.

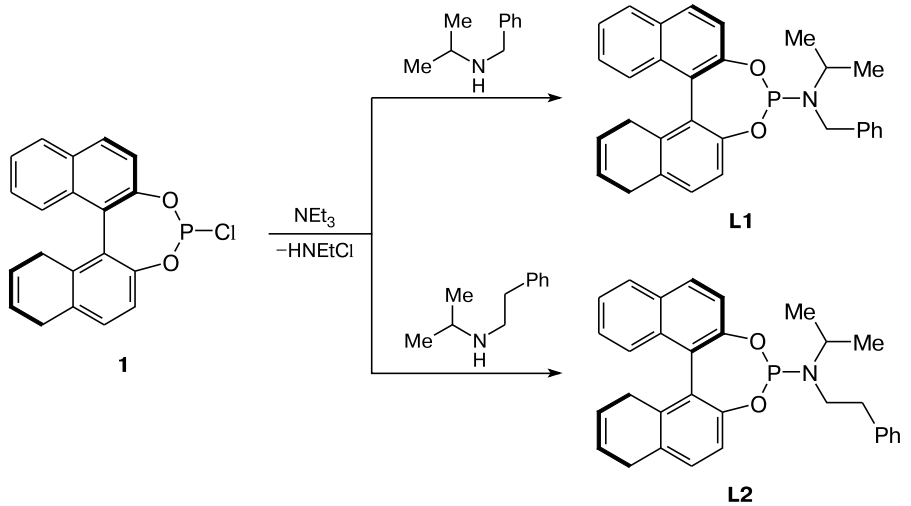
Key words: enantioselective hydrogenation, rhodium complexes, iridium complexes, enamides, benzodiazepinones, amidophosphites.

Lately, much attention is paid to the development of catalyst systems based on metal complexes for carrying out asymmetric hydrogenation reactions.[1] Inexpensive hydrogen and small amounts of catalyst make this process promising. The known examples of metal complex hydrogenation of unsaturated precursors mainly include the use of expensive chiral phosphine ligands.[2—4] A convenient alternative to phosphine systems are phosphite-type ligands, which can be obtained over several tens of minutes from available reagents. Chiral phosphites and amidophosphites showed bright results in a number of processes of asymmetric hydrogenation.[5] In this connection, the search for simple, but efficient metal complex catalysts based on such ligands for asymmetric hydrogenation of unsaturated precursors seems an actual issue. In the present work, we report on the synthesis of new amidophosphite ligands, as well as on their application in asymmetric hydrogenation, which yielded nonnatural amino acids and tetrahydro-1*H*-benzodiazepinones exhibiting asthmatic, anticancer, neuroprotective properties.[6—9] Note that the information on the synthesis of tetrahydro-1*H*-benzodiazepinones by asymmetric hydrogenation is absent in the scientific literature. There are only examples of their preparation by hydrosilylation and Hantzsch reduction.[10,11]

Results and Discussion

The reaction of the chiral phosphorylating agent **1** with *N*-benzyl-*N*-isopropylamine or *N*-isopropyl-*N*-(2-phenylethyl)amine in CH_2Cl_2 was used to synthesize new amidophosphite ligands **L1** and **L2** (Scheme 1).

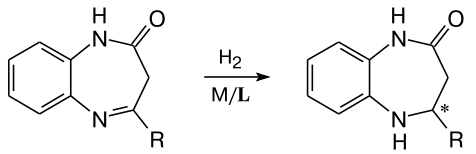
Scheme 1



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1213—1216, July, 2017.

The efficiency of these amidophosphites was initially tested in the Ir-catalyzed hydrogenation of benzodiazepinone **2a** (Scheme 2). When ligands **L1** and **L2** were used in CH_2Cl_2 as the solvent, the conversion was moderate (Table 1, entries *1* and *2*). The hydrogenation in ethanol provided a complete conversion when **L1** was used (entry *3*).

Scheme 2



2a,b **3a,b**

R = Ph (**a**), Me (**b**)

We checked a suggestion of using a combination of chiral phosphite ligands with achiral phosphines in hydrogenation of compound **2a**. Such an approach has been already used in hydrogenation and in a number of cases considerably increased enantioselectivity.[12–14] The use of a mixture of ligands **L1** or **L2** in a combination with triphenylphosphine in CH_2Cl_2 gave the product with 24% *ee*, while a better conversion was shown by ligand **L1** (see Table 1, entries *4* and *5*). In the case of **L1**, replacement of CH_2Cl_2 with ethanol allowed us to reach 50% *ee* (entry *6*). The use of tricyclohexylphosphine as an additive to **L1** led to a decrease in enantioselectivity (see Table 1, entries *7* and *8*). The compound $[Ir(COD)_2]$BARF (BARF is the tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was also tested as a precatalyst and showed a low efficiency (see Table 1, entry *9*).

A complete conversion was reached in the Ir-catalyzed hydrogenation of benzodiazepinone **2b** (see Scheme 2) involving ligands **L1** and **L2** in CH_2Cl_2, with the higher selectivity being shown by amidophosphite **L1** (Table 2, entries *1* and *2*). In ethanol, **L1** gave almost racemic product (entry *3*). The addition of triphenylphosphine to **L1** and **L2** considerably increased the enantioselectivity (*cf.* entries *1*, *2* and *4*, *5*). The use of ethanol in the case of **L1** in the combination with triphenylphosphine showed similar results (see Table 2, entry *6*). The use of a mixture of **L1** and tricyclohexylphosphine gave a racemate (see Table 2, entry *7*). The involvement of an alternative precatalyst $[Ir(COD)_2]$BARF and **L1** gave the product with 44% *ee* without phosphine additives.

Table 1. Metal complex hydrogenation of compound **2a**[a]

Entry	Catalyst system[b]	Solvent	Conversion (%)	*ee* (%)[c]
1	**A**/4**L1**	CH_2Cl_2	30	0
2	**A**/4**L2**	CH_2Cl_2	26	0
3	A/4**L1**	EtOH	100	0
4	**A**/2**L1**/2PPh_3	CH_2Cl_2	63	24(+)
5	**A**/2**L2**/2PPh_3	CH_2Cl_2	21	24(+)
6	**A**/2**L1**/2PPh_3	EtOH	67	50(+)
7	**A**/2**L1**/2PCy_3	EtOH	43	8(+)
8	**A**/2**L1**/2PCy_3	CH_2Cl_2	27	6(+)
9	**B**/2**L1**	CH_2Cl_2	20	28(+)

[a] $T = 25$ °C, $P(H_2) = 55$ atm, $\tau = 24$ h, $[Ir(COD)Cl]_2$/**2a** = 1/200.
[b] **A** = $[Ir(COD)Cl]_2$, **B** = $[Ir(COD)_2]$BARF.
[c] The sign of the product specific rotation is given in parentheses.

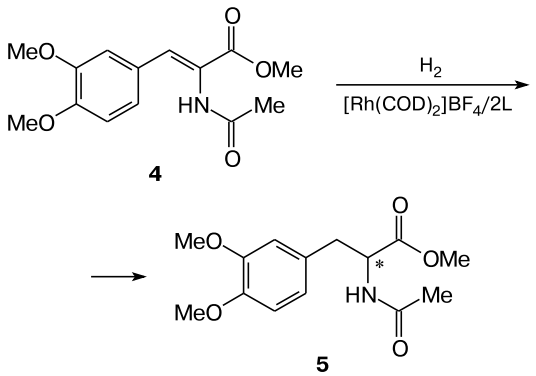
Table 2. Metal complex hydrogenation of compound **2b**[a]

Entry	Catalyst system[b]	Solvent	Conversion (%)	*ee* (%)[c]
1	**A**/4**L1**	CH_2Cl_2	100	22(+)
2	**A**/4**L2**	CH_2Cl_2	100	12(+)
3	**A**/4**L1**	EtOH	95	6(+)
4	**A**/2**L1**/2PPh_3	CH_2Cl_2	100	50(+)
5	**A**/2**L2**/2PPh_3	CH_2Cl_2	100	26(+)
6	**A**/2**L1**/2PPh_3	EtOH	100	47(+)
7	**A**/2**L1**/2PCy_3	CH_2Cl_2	100	0
8	**B**/2**L1**	CH_2Cl_2	100	44(+)

[a] $T = 25$ °C, $P(H_2) = 55$ atm, $\tau = 24$ h, $[Ir(COD)Cl]_2$/**2b** = 1/200.
[b] **A** = $[Ir(COD)Cl]_2$, **B** = $[Ir(COD)_2]$BARF.
[c] The sign of the product specific rotation is given in parentheses.

Ligands **L1** and **L2** were tested in the Rh-catalyzed hydrogenation of methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**) which yielded an *L*-DOPA derivative (Scheme 3).

Scheme 3



Like in the case with heterocyclic substrates **2a**,**b**, amidophosphite **L2** showed a lower efficiency (Table 3, entries *1* and *2*). The use of **L1** in a combination with triphenylphosphine increased the enantioselectivity (see Table 3, *cf.* entries *1* and *3*), similarly to the case of hydrogenation of substrates **2a**,**b**.

Table 3. Metal complex hydrogenation of compound **4***

Entry	Catalyst system	Conversion (%)	*ee* (%)
1	$[Rh(COD)_2]BF_4$/**2L1**	100	58 (*S*)
2	$[Rh(COD)_2]BF_4$/**2L2**	50	54 (*S*)
3	$[Rh(COD)_2]BF_4$/**L1**, PPh_3	100	72 (*S*)

* $T = 50$ °C, $P(H_2) = 55$ atm, $\tau = 2$ h, CH_2Cl_2, $[Rh(COD)_2]BF_4$/**4** = = 1/100.

This effect was also confirmed for the structurally similar substrate, namely, methyl (*Z*)-2-acetamido-4-(4-fluorophenyl)acrylate (**6**, Scheme 4). Thus, the use of **L1** provided 58% *ee*, which grew to 80% when triphenylphosphine was added (Table 4).

Scheme 4

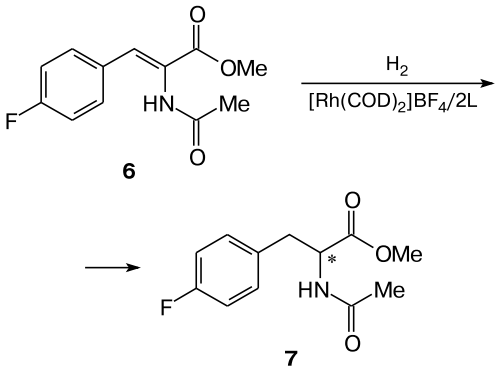


Table 4. Metal complex hydrogenation of compound **6***

Entry	Catalyst system	Conversion (%)	*ee* (%)
1	$[Rh(COD)_2]BF_4$/**2L1**	100	58 (*S*)
2	$[Rh(COD)_2]BF_4$/**L1**, PPh_3	100	80 (*S*)

* $T = 50$ °C, $P(H_2) = 55$ atm, $\tau = 2$ h, CH_2Cl_2, $[Rh(COD)_2]BF_4$/**6** = = 1/100.

In conclusion, we accomplished the synthesis of new chiral amidophosphites, tested them in the reactions of Ir-catalyzed hydrogenation of 1,5-benzodiazepinones and Rh-catalyzed hydrogenation of dehydro amino acid derivatives. We showed that the addition of triphenylphosphine can considerably increase the enantioselectivity of hydrogenation of the substrates tested.

Experimental

^1H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (400.13, 161.98, and 100.6 MHz) relative to Me_4Si and 85% H_3PO_4 in D_2O, respectively. The phosphorylating agent (R_a)-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*]-[1,3,2]dioxaphosphepane (**1**),[15] *N*-benzyl-*N*-isopropylamine,[16] *N*-isopropyl-*N*-(2-phenylethyl)amine,[17] $[Ir(COD)Cl]_2$,[18] $[Ir(COD)_2]BARF$,[19] $[Rh(COD)_2]BF_4$,[20] 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**2a**),[21] methyl (*Z*)-2-acetamido-3-(3,4-dimethoxyphenyl)acrylate (**4**),[22] and methyl (*Z*)-2-acetamido-4-(4-fluorophenyl)acrylate (**6**)[23] were obtained according to the procedure described in the literature.

Synthesis of ligands L1 and L2 (general procedure). *N*-Benzyl-*N*-isopropylamine or *N*-isopropyl-*N*-(2-phenylethyl)amine (1.4 mmol) and NEt_3 (1.6 mmol, 0.22 mL) in CH_2Cl_2 (10 mL) were added to a solution of (R_{ax})-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (**1**) (0.5 g, 1.4 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 20 min at room temperature and washed with water (20 mL) to remove $HNEt_3Cl$. The organic layer was separated, dried with Na_2SO_4, and passed through a layer of silica gel, the solvent was removed *in vacuo*.

(R_a)-2-(*N*-Benzyl-*N*-isopropylamino)dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (L1). The yield was 0.526 g (81%), a white powder, m.p. 110—111 °C. $[\alpha]_D = 441.2$ (*c* 1.0, $CHCl_3$). Found (%): C, 77.78; H, 5.61; N, 2.96. $C_{30}H_{26}NO_2P$. Calculated (%): C, 77.74; H, 5.65; N, 3.02. $^{31}P\{H\}$ NMR ($CDCl_3$), δ: 147.43. ^1H NMR ($CDCl_3$), δ: 1.18 (d, 3 H, J = 8 Hz); 1.31 (d, 3 H, J = 8 Hz); 3.47 (m, 1 H); 3.67 (m, 1 H); 4.21 (m, 1 H); 7.23—7.52 (m, 12 H); 7.63 (d, 1 H, J = 8 Hz); 7.94—7.99 (m, 3 H); 8.02 (d, 1 H, J = 8 Hz). ^{13}C NMR ($CDCl_3$), δ: 23.01 (d, $J_{C,P}$ = = 10 Hz); 23.68 (d, $J_{C,P}$ = 6 Hz); 39.53; 46.85 (d, $J_{C,P}$ = 6 Hz); 48.53 (d, $J_{C,P}$ = 20 Hz); 121.91, 122.32, 123.33, 124.12, 124.17, 124.57, 124.81, 126.08, 126.79, 127.06, 127.12, 127.83, 128.16, 128.28, 128.38, 130.00, 130.29, 130.72, 131.45, 132.70, 132.89, 140.76, 149.7; 150.14 (d, $J_{C,P}$ = 4 Hz).

(R_a)-2-[*N*-Isopropyl-*N*-(2-phenylethyl)amino]dinaphtho-[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (L2). The yield was 0.528 g (79%), a white powder, m.p. 105—106 °C. $[\alpha]_D = 438.0$ (*c* 1.0, $CHCl_3$). Found (%): C, 77.92; H, 5.98; N, 2.89. $C_{31}H_{28}NO_2P$. Calculated (%): C, 77.97; H, 5.91; N, 2.93. $^{31}P\{H\}$ NMR ($CDCl_3$), δ: 153.22. ^1H NMR ($CDCl_3$), δ: 1.39 (s, 3 H); 1.41 (s, 3 H); 2.74 (m, 1 H); 3.01 (m, 3 H); 3.79 (m, 1 H); 6.79—7.68 (m, 13 H); 7.96—8.10 (m, 4 H). ^{13}C NMR ($CDCl_3$), δ: 23.38 (d, $J_{C,P}$ = 6 Hz); 23.6 (d, $J_{C,P}$ = 7 Hz); 39.53; 44.8; 48.53 (d, $J_{C,P}$ = 30 Hz); 122.21, 122.29, 122.41, 124.19, 124.22, 124.62, 124.9, 126.00, 126.24, 126.27, 127.06, 127.15, 128.24, 128.45, 128.51, 128.51, 130.06, 130.41, 130.83, 131.52, 133.02, 139.78, 149.91; 150.53 (d, $J_{C,P}$ = 6 Hz).

4-Methyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (2b). Triethylamine (16.7 mL, 0.12 mol) was added dropwise to a solution of acetyl chloride (7.8 g, 0.1 mol) in diethyl ether (100 mL) cooled with an ice-water bath under argon over 30 min and the resulting mixture was stirred for 1 h. A solution of 1,2-diaminobenzene (4.3 g, 0.04 mol) in acetonitrile (50 mL) was added dropwise to the diketene formed, which is unstable at room temperature and toxic. After stirring over 1 h in an ice-water bath, the mixture was allowed to stand at room temperature for 8 h. Then, the reaction mixture was worked-up with water (30 mL), the product was extracted with ethyl acetate (3×25 mL). The organic phase was dried with sodium sulfate, the solvent was removed *in vacuo*. The product was purified by recrystallization from ethyl acetate. The yield was 38%. The spectral characteristics of **2b** correspond to the literature data.[24]

Asymmetric hydrogenation of compounds 2a,b. A corresponding ligand (0.012 mmol or 0.024 mmol) or a chiral and an achiral ligands (0.012 mmol each) in CH_2Cl_2 (0.5 mL) were added to a solution of $[Ir(COD)_2]BARF$ (7.6 mg, 0.006 mmol) or dimeric $[Ir(COD)Cl]_2$ (4 mg, 0.006 mmol) and the resulting mixture was stirred for 5 min with a magnetic stirrer. The solvent was removed *in vacuo*. Ethanol or CH_2Cl_2 (4 mL and **2a** or **2b** (0.3 mmol) were added to the obtained catalyst, an autoclave was filled with hydrogen (55 atm) and the experiments were carried out at room temperature with stirring using with a magnetic stirrer. After decompression, the reaction mixture was diluted with CH_2Cl_2 (2 mL) and purified from the catalyst by filtration through a short layer of silica gel, the solvents were removed *in vacuo*. The enantiomeric composition was determined by HPLC, using a Kromasil 3-AmyCoat column (UV 219 nm, hexane/isopropyl alcohol = 90/10, 1 mL min^{-1}). The retention times for the enantiomers of 4-phenyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one are 17.4 ((−)-**3a**) and 19.3 min ((+)-**3a**) and for 4-phenyl-1,3-dihydro-2*H*-1,5-benzodiazepin-2-one (**2a**) it is 9.1 min. The retention times for the enantiomers of 4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one are16.5 ((−)-**3b**) and 23.4 min ((+)-**3b**) and for **1b** it is 6.6 min. The conversion of **2a** and **2b** was determined using ^1H NMR spectroscopy. Spectral characteristics of products **3a** and **3b** correspond to those published earlier.[25]

Asymmetric hydrogenation of compounds 4 and 6. A solution of $[Rh(COD)_2]BF_4$ (2 mg, 0.005 mmol) in a solvent (0.5 mL) and ligand **L1**, **L2** (0.01 mmol) or a mixture of a chiral ligand (0.005 mmol) and triphenylphosphine (0.005 mmol) in CH_2Cl_2 (1 mL) were placed into a 10-mL autoclave, the reaction mixture was stirred for 2 min, followed by the addition of the substrate **4** or **6** (0.5 mmol) in the corresponding solvent (2 mL). The autoclave was filled with hydrogen (55 atm) and heated to 50 °C (10 min). The process was carried out for 2 h with magnetic stirring. After the reaction reached completion, the autoclave was cooled to room temperature, the reaction mixture was purified from the catalyst by filtration through a short layer of silica gel, the solvent was removed *in vacuo*. Spectral characteristics of products **5** and **7** correspond to the literature data.[26] The enantiomeric excess of **5** and **7** was determined by HPLC on Chiralcel OJ-H and Kromasil 5-Amycoat columns according to the procedure described in the literature.[6,22]

This work was financially supported by the Russian Foundation for Basic Research (Project No. 17-03-00483).

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Received March 20, 2017;
in revised form June 8 , 2017