Synthesis of new amidophosphite ligand and its application in Ir-catalyzed asymmetric hydrogenation of heterocyclic compounds

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A new chiral amidophosphite ligand was synthesized and tested in the iridium-catalyzed hydrogenation of heterocyclic compounds. The enantioselectivity of hydrogenation of 2-methylquinoline considerably increases when piperidine hydrochloride is used as an additive. The hydrogenation reaction of 8-methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole by metal complex was conducted for the first time to prepare enantiomerically enriched antidepressant Pyrazidol.

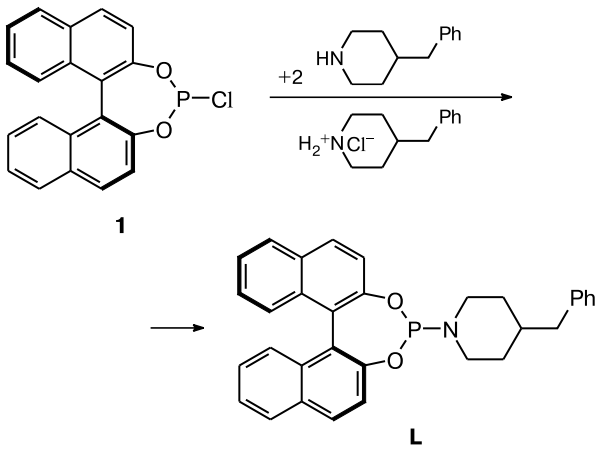
Key words: asymmetric hydrogenation, amidophosphite, iridium, heterocyclic compounds.

Heterocyclic compound are a leading class of organic substances in terms of the number of compounds possessing medicinal properties.[1,2] Recently, the replacement of synthetic racemic heterocyclic compounds by optically active specimenss became an actual problem of medical chemistry. The latter is a consequence of a possible negative influence of one of the enantiomers present in the racemate on the patient´s organism.[3] One of the attractive approaches to the preparation of chiral heterocyclic compounds is the catalytic hydrogenation of cyclic prochiral imines by metal complex. This one-step process uses the cheapest reducing agent molecular hydrogen and a small amount of the catalyst.[4] Heterocyclic compounds themselves are ligands due to the presence of the electron-donating atoms, such as nitrogen, that can lead to the saturation of the vacant orbitals of the catalytically active metal and deactivation of the hydrogenation catalyst. In addition, many heterocycles are aromatic compounds, and the aromaticity additionally hinders the formation of the chiral center because of the transformation of the aromatic ring into the aliphatic.[5] In the pioneering studies by Murata on hydrogenation of heterocyclic compounds in the presence of metal complexes with the phosphine ligands, a low enantioselectivity was obtained (2% *ee*). Later, successful works were carried out on the use of chiral phosphines in the hydrogenation of a wide series of prochiral heterocycles.[4,6] A large-scale preparation of phosphine ligands is difficult enough, because this multistep process requires a modern technique in handling sensitive reagents, such as butyllithium. Little attention was paid to the use of more available phosphite-type ligands in this process. So far, only three works on the use of this group of ligands in the Ir-catalyzed hydrogenation of heterocyclic compounds have been published.[7—9] In the present work, we report the synthesis of a new chiral amidophosphite ligand and its use in the Ir-catalyzed hydrogenation of 2-methylquinoline and 8-methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole.

Results and Discussion

The new amidophosphite ligand **L** was obtained by the one-step reaction of phosphorylating agent **1** with 4-benzylpiperidine (Scheme 1).

Scheme 1



At the beginning, the efficiency of amidophosphite **L** was studied in the Ir-catalyzed hydrogenation of 2-methylquinoline (**2**) (Scheme 2) in various organic solvents at

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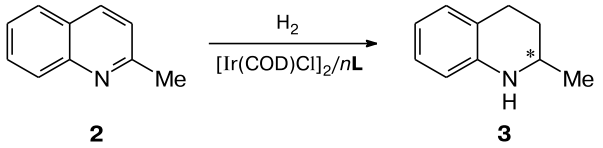
20 °C with the *in situ* formation of the catalysts derived from $[Ir(COD)Cl]_2$.

Scheme 2

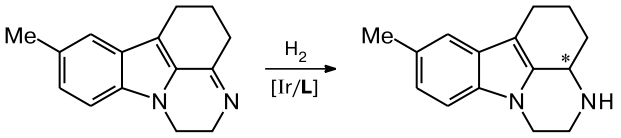


2 **3**

It was found that for the molar ratio Ir/L = 1/2, the highest conversion and enantioselectivity were observed in dichloromethane (Table 1, entries *1—3*). The change in the molar ratio to Ir/L = 1/1 decreased the conversion and the enantiomeric excess of the reaction product **3** (see Table 1, entries *3* and *4*). In an attempt to improve the obtained results, molecular iodine was added to the catalyst. This resulted in the increase of both the conversion and the enantiomeric excess of the reaction product in all the solvents studied (see Table 1, entries *1—3* and *5—7*). The addition of iodine to the catalyst led to the inversion of the absolute configuration of the product obtained. This effect, most likely, can be explained by the change in the structure of metal complex caused by the transformation of the catalytically active species Ir^{I} into Ir^{III} in the reaction with iodine, a characteristic feature of similar catalysts containing phosphine ligands.[4] Recently, the enantiomeric excess of the iridium-catalyzed hydrogenation of heterocyclic compounds involving the phosphine and phosphite ligands was also increased in the presence of amine hydrochlorides as additives.[10] We have chosen piperidine hydrochloride as such additive. In this case, the enantiomeric excess of the reaction product in fact was higher as compared to the results obtained without such additives (see Table 1, entries *1—3* and *8—10*), however, the lost of the catalyst activity was observed. In order to increase conversion, the temperature of the reaction mixture was increased from 20 to 50 °C, which resulted in the expected increase of conversion and enantiomeric excess of the reaction product (see Table 1, entries *11—13*). The latter interesting fact can be explained by the increase in the solubility of piperidine hydrochloride, as well as by the facilitation the reverse transfer of the hydrochloride protection from piperidine to the nitrogen atom of 2-methylquinoline, that increases the selectivity of hydrogenation.

The efficiency of amidophosphite ligand **L** was also studied in the Ir-catalyzed asymmetric hydrogenation of 8-methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (**4**) to 8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (**5**, Scheme 3), which is an active substance of the antidepressant Pyrazidol (Pyrlindole).[11] The *in situ* formation of the catalyst from $[Ir(COD)Cl]_2$ resulted in a moderate conversion, whereas enantioselectivity was observed only in dichloromethane (Table 2, entries *1—3*). The use of iodine and piperidine hydrochloride as additives allowed us to increase the activity of the catalyst, however, the enantioselectivity of the process decreased (see Table 2, entries *3* and *4*, *5*). The use of $[Ir(COD)_2]BARF$ (BARF stands for tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) as a pre-catalyst allowed us to reach a complete conversion within 24 h and obtain 22% *ee* (see Table 2, entries *6* and *7*). However, the introduction of the iodine and piperidine hydrochloride addi-

Scheme 3



4 **5**

Table 1. Asymmetric hydrogenation of 2-methylquinoline (**2**) (pressure of H_2 35 atm, 24 h)

Entry	Catalyst	Solvent	Additive	*T*/°C	Conversion (%)	*ee* (%)
1	$[Ir(COD)Cl]_2$/4**L**	THF	—	20	32	2 (*S*)
2	$[Ir(COD)Cl]_2$/4**L**	Toluene	—	20	37	4 (*S*)
3	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	—	20	48	18 (*S*)
4	$[Ir(COD)Cl]_2$/2**L**	CH_2Cl_2	—	20	36	5 (*S*)
5	$[Ir(COD)Cl]_2$/4**L**	THF	I_2	20	100	20 (*R*)
6	$[Ir(COD)Cl]_2$/4**L**	Toluene	I_2	20	62	10 (*R*)
7	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	I_2	20	100	30 (*R*)
8	$[Ir(COD)Cl]_2$/4**L**	THF	*	20	6	4 (*S*)
9	$[Ir(COD)Cl]_2$/4**L**	Toluene	*	20	25	15 (*S*)
10	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	*	20	30	30 (*S*)
11	$[Ir(COD)Cl]_2$/4**L**	THF	*	50	32	38 (*S*)
12	$[Ir(COD)Cl]_2$/4**L**	Toluene	*	50	49	35 (*S*)
13	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	*	50	57	**51** (*S*)

* Piperidine hydrochloride.

Table 2. Asymmetric hydrogenation of **4** (pressure of H_2 35 atm, 24 h)

Entry	Catalyst	Solvent	Additive	*T*/°C	Conversion (%)	*ee* (%)
1	$[Ir(COD)Cl]_2$/4**L**	THF	—	20	34	0
2	$[Ir(COD)Cl]_2$/4**L**	Toluene	—	20	38	0
3	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	—	20	49	17
4	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	I_2	20	62	10
5	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	*	20	70	0
6	$[Ir(COD)_2]$BARF/2**L**	CH_2Cl_2	—	20	100	22
7	$[Ir(COD)_2]$BARF/2**L**	Toluene	—	20	100	10
8	$[Ir(COD)_2]$BARF/2**L**	CH_2Cl_2	I_2	20	64	14
9	$[Ir(COD)_2]$BARF/2**L**	CH_2Cl_2	*	20	37	0

* Piperidine hydrochloride.

tives resulted in the decrease of conversion and enantioselectivity of the process (see Table 2, entries *8*, *9*).

In conclusion, we synthesized a new amidophosphite ligand and tested it in the iridium-catalyzed hydrogenation of heterocyclic compounds. In the case of hydrogenation of 2-methylquinoline, enantioselectivity considerably increased when piperidine hydrochloride was used as an additive. We were the first to show a possibility of hydrogenation of 8-methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole by the metal complex catalysts. Despite a low enantioselectivity, in future this approach can open access to the one-step and enantioselective preparation of antidepressant Pyrazidol.

Experimental

^1H, ^{13}C, ^{31}P NMR spectra were recorded on a Bruker Avance 600 spectrometer (600.15 MHz) relative to Me_4Si. The phosphorylating agent (S_{ax})-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (**1**),[12] as well as $[Ir(COD)_2Cl]_2$,[13] $[Ir(COD)_2]$BARF,[14] 8-methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole[15] were obtained according to the published procedures. 4-Benzylpiperidine and 2-methylquinoline are commercially available compounds (Aldrich).

Synthesis of (S_{ax})-2-[3-(4-benzyl)piperidin-1-yl](dinaphtho-[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (L). 4-Benzylpiperidine (0.491 g, 2.8 mmol) in C_6H_6 (10 mL) was added to a solution of (S_{ax})-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepane (**1**) (0.5 g, 1.4 mmol) in C_6H_6 (15 mL). The reaction mixture was heated to boiling and cooled to room temperature, a precipitate of 4-benzylpiperidine hydrochloride was filtered off. The solution obtained was subjected to flash-chromatography on silica gel (eluent benzene). The solvent was evaporated *in vacuo*. The yield was 0.582 g (85%), white powder, m.p. 85—87 °C. Found (%): C, 78.59; H, 5.82; N, 2.79. $C_{27}H_{19}O_4P$. Calculated (%): C, 78.51; H, 5.77; N, 2.86. $^{31}P\{H\}$ NMR ($CDCl_3$), δ: 145.6 (s). ^1H NMR ($CDCl_3$)), δ: 1.06 (m, 1 H, β-H_b, piperidine); 1.18 (m, 1 H, β′-H_b, piperidine); 1.43 (m, 1 H, β-H_a, piperidine); 1.62 (m, 1 H, β′-H_a, piperidine); 1.64 (m, 1 H, γ-H, piperidine); 2.38 (m, 1 H, α-H_b, piperidine); 2.54 (m, 1 H, CH_2); 2.76 (m, 1 H, α′-H_b, piperidine); 3.30 (m, 1 H, α-H_a, piperidine); 3.51 (m, 1 H, α′-H_a, piperidine); 7.13 (d, 2 H, *o*-H_{Ph}, $J_{H,H}$ = 7.0 Hz); 7.21 (t, 1 H, *p*-H_{Ph}, $J_{H,H}$ = 7.3 Hz); 7.29 (m, 4 H, *m*-H_{Ph}, H(7), H(7′)); 7.37 (d, 1 H, H(8′), $J_{H,H}$ = 8.5 Hz); 7.40 (d, 1 H, H(3), $J_{H,H}$ = = 8.4 Hz); 7.44 (m, 3 H, H(6), H(6′), H(8)); 7.56 (d, 1 H, H(3′), $J_{H,H}$ = 8.7 Hz); 7.92 (d, 1 H, H(4), $J_{H,H}$ = 9.2 Hz); 7.95 (d, 2 H, H(5), H(5′), $J_{H,H}$ = 9.6 Hz); 8.00 (d, 1 H, H(4′), $J_{H,H}$ = = 9.2 Hz). $^{13}C\{H\}$ NMR ($CDCl_3$), δ: 33.1 (β′-C, piperidine); 33.4 (β-C, piperidine); 38.5 (γ-C, piperidine); 43.5 (CH_2); 45.1 (α′-C, piperidine); 45.3 (α-C, piperidine); 122.1 (C(3′)); 122.2 (C(3)); 122.7 (C(1)); 123.9 (C(1′)); 124.6 (C(6′)); 124.8 (C(6)); 125.9 (*p*-C_{Ph}); 126.1 (C(7)); 126.1 (C(7′)); 127.0 (C(8)); 127.0 (C(8′)); 128.2 (*m*-C_{Ph}); 128.3 (C(5), C(5′)); 128.4 (C(3)); 129.2 (*o*-C_{Ph}); 129.9 (C(4)); 130.3 (C(4′)); 130.7 (C(10)); 131.4 (C(10′)); 132.6 (C(9)); 132.8 (C(9′)); 140.3 (*ipso*-C_{Ph}); 149.6 (C(2′)); 149.9 (C(2)).

Asymmetric hydrogenation of 2-methylquinoline (2) (general procedure). The ligand (0.024 or 0.012 mmol, see Table 1) in CH_2Cl_2 (0.2 mL) was added to $[Ir(COD)Cl]_2$ (4 mg, 0.006 mmol) in CH_2Cl_2 (0.2 mL), and the mixture was stirred for 5 min, followed by the addition of the corresponding additive (0.06 mmol) and additional stirring for 10 min on a magnetic stirrer in a 10-mL autoclave. The solvent was evaporated *in vacuo*. 2-Methylquinoline (**2**) (86 mg, 0.6 mmol) in the corresponding solvent (1.5 mL) (see Table 1) was added to the catalyst obtained. The sealed autoclave was filled with hydrogen (35 atm), heated to the proper temperature (10 min), and the experiments were carried out with stirring on a magnetic stirrer. After the hydrogen was released, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and purified from the catalyst by passing through a short layer of silica gel, the solvents were evaporated *in vacuo*. Conversion of **2** was measured by ^1H NMR. The optical yield of **3** was determined by HPLC on an Agilent HP-1100 chromatograph with a Chiralcel OJ-H column following the known recommendations.[16] The absolute configuration of enantiomers **3** was found by comparing the measured optical rotation with the literature data.[17]

Asymmetric hydrogenation of 8-methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (4) (general procedure). The ligand (0.0044 or 0.0088 mmol) in CH_2Cl_2 (0.2 mL) was added to the corresponding (see Table 2) iridium precursor (0.0022 mmol) in CH_2Cl_2 (0.1 mL), the mixture was stirred for 5 min, followed by the addition of the corresponding additive (0.22 mmol) and additional stirring for 10 min on a magnetic stirrer in a 10-mL autoclave. The solvent was evaporated *in vacuo*. 8-Methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*jk*]carbazole (**4**) (49 mg, 0.22 mmol) in the corresponding solvent (1 mL) was added to the catalyst obtained. The sealed autoclave was filled with hy-

drogen (35 atm), heated to the desired temperature (10 min), and the experiments were carried out with stirring on a magnetic stirrer. After hydrogen was released, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and separated from the catalyst by passing through a short layer of silica gel, the solvents were evaporated *in vacuo*. Conversion of **4** was measured by NMR.[18] The optical yield of **5** was determined by HPLC on an Agilent HP-1100 chromatograph with a Chiralcel OD-H column (250×4.6 mm, UV irradiation, λ = 260 nm, a mixture of hexane : isopropanol : diethylamine = 95 : 5: 0.1, 0.9 mL min^{-1}). The retention times for enantiomers **6** were 14.5 min ((+)-isomer) and 16.0 min ((−)-isomer), for substrate **4**, 10.8 min.

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