New ionic phosphite ligands: synthesis and application in asymmetric Rh-catalyzed hydrogenation

S. E. Lyubimov, P. V. Petrovskii, 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

A series of chiral ionic phosphite-type ligands bearing pyridinium and imidazolium fragments were prepared. Testing of these ligands in Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate resulted in 95% *ee* of the products with 100% conversion of the reactants.

Key words: ionic phosphites, rhodium complexes, asymmetric hydrogenation.

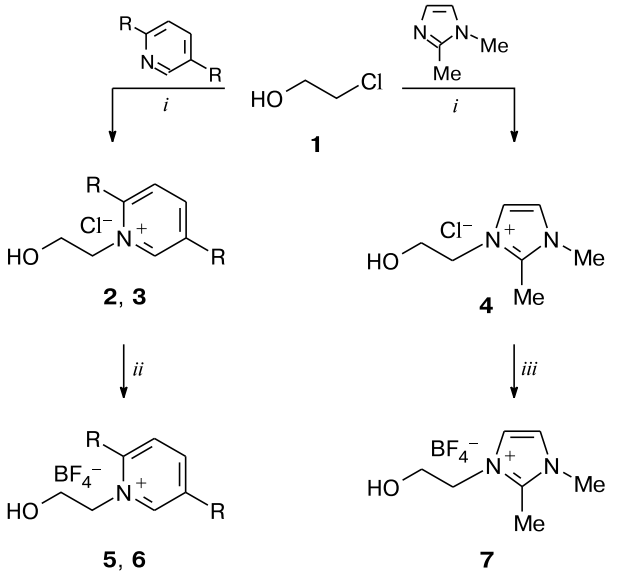
Catalytic asymmetric hydrogenation of prochiral olefins is a convenient approach to the synthesis of valuable optically active compounds due to low cost of molecular hydrogen, rather high reaction rates, and low catalyst consumption.[1,2] Most of the currently known effective chiral ligands, including those used in industry, are bidentate phosphines.[2] Relatively recently, it was shown that the use of synthetically more accessible monodentate phosphite and amidophosphite ligands also provides high enantiomeric excess values (>99% *ee*) at 100% conversion of the reactants in asymmetric hydrogenation.[3—6] A promising group of monodentate ligands is the group of ionic chiral phosphites and diamidophosphites that we developed. These compounds synthesized on the basis of imidazolium ionic liquids and quaternized amino alcohols provide high asymmetric induction both in asymmetric hydrogenation and in allylic substitution reactions (up to 99% *ee*).[7—9] An interesting task is the search for other effective catalytic systems based on the cationic phosphite-type ligands and their testing in asymmetric catalytic reactions.

Here we describe the synthesis of new ionic phosphite ligands comprising one-step phosphorylation of pyridinium and imidazolium ionic liquids and their use in Rh-catalyzed asymmetric hydrogenation.

Results and Discussion

Hydroxyl-containing ionic liquids **5**—**7** were prepared by quaternization of readily accessible compounds such as pyridine, 2,5-dimethylpyridine, and 1,2-dimethylimidazole with 2-chloroethanol (**1**) followed by replacement of the counter-ion by tetrafluoroborate in the intermediates **2**—**4** (Scheme 1).

Scheme 1



R = H (**2**, **5**), Me (**3**, **6**)
i. 150 °C, 2 h. *ii*. KBF_4, Me_2CO/EtOH, 72 h. *iii*. KBF_4, Me_2CO, 72 h.

Novel chiral ionic phosphites **9**—**11** were prepared by one-step phosphorylation of hydroxyl-containing pyridinium (**5**, **6**) and imidazolium (**7**) ionic liquids in CH_2Cl_2 (Scheme 2). All ligands **9**—**11** are readily soluble in polar organic solvents such as CH_2Cl_2, $CHCl_3$, acetonitrile and are stable on long-term storage in a dry atmosphere.

We studied the reactions of phosphites **9**—**11** with $[Rh(COD)_2]BF_4$ (COD is cycloocta-1,5-diene). Ligands **9** and **11** are coordinated in the monodentate mode to give complexes $[Rh(COD)L_2]BF_4$ (Scheme 3), which was

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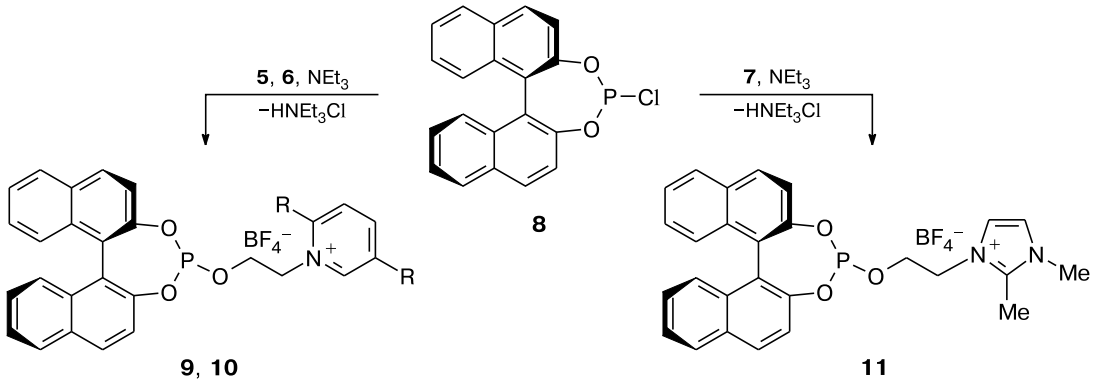
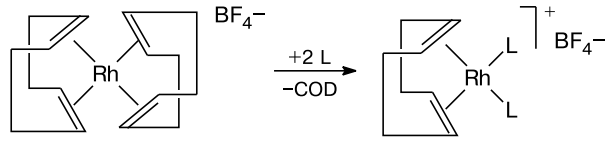
Scheme 2



confirmed by ^{31}P NMR data and by elemental analysis. Conversely, phosphite **10** shows nonselective coordination as indicated by two doublets (δ_1 = 125.9, d, $J_{P,Rh}$ = 260.0 Hz, 61% and δ_2 = 140.9, d, $J_{P,Rh}$ = 207.4 Hz, 39%) in the ^{31}P NMR spectrum of the isolated complex. Probably, this is caused by steric reasons.

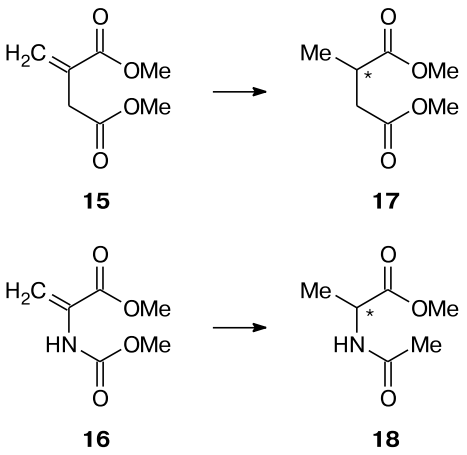
Scheme 3



12, **13**, **14**

L = **9**, **10**, **11**

Scheme 4



15 **17**

16 **18**

Conditions: H_2 (5 atm), CH_2Cl_2, cat*.

The efficiency of novel ionic catalytic systems containing phosphites **9**—**11** and complexes **12** and **14** was tested in Rh-catalyzed asymmetric hydrogenation of methyl esters of prochiral unsaturated acids: dimethyl itaconate (**15**) and methyl 2-acetamidoacrylate (**16**) (Scheme 4); the results are summarized in Table 1.

In the case of ligands **9** and **11**, quantitative conversion for both substrates (**15** and **16**) at low hydrogen pressure (5 atm) and, in addition, high enantiometric excesses (92—95% *ee*) were achieved. Note that the process enantioselectivity does not change on using the catalysts formed *in situ* from ligands **9** and **11** or the isolated complexes **12** and **14** (see Table 1, runs *1*, *2*, and *4*—*9*). The

Table 1. Asymmetric hydrogenation of dimethyl itaconate **12** and methyl 2-acetamidoacrylate **14** (5 atm H_2, CH_2Cl_2)

Run	Catalyst	Substrate	*t*/h	Conversion[a]	*ee* (%)[b,c]
1	[Rh(COD)L_2]BF_4/**9**	**15**	16	100	94 (*R*)
2	**12**	**15**	15	100	95 (*R*)
3	[Rh(COD)L_2]BF_4/**10**	**15**	20	95	70 (*R*)
4	[Rh(COD)L_2]BF_4/**11**	**15**	16	100	94 (*R*)
5	**14**	**15**	16	100	94 (*R*)
6	[Rh(COD)L_2]BF_4/**9**	**16**	16	100	93 (*S*)
7	**12**	**16**	16	100	94 (*S*)
8	[Rh(COD)L_2]BF_4/**11**	**16**	16	100	92 (*S*)
9	**14**	**16**	16	100	94 (*S*)

[a] Determined by ^1H NMR.

[b] The enantiomeric excess of **17** was determined by HPLC, Chiralcel OD-H column, C_6H_{14}/Pr^iOH = 98/2, 0.8 mL min^{-1}, 219 nm, t_R 9.21 min, t_S 16.14 min. The absolute configuration of product **17** was determined with account of the optical rotation sign.

[c] The enantiomeric excess of **18** was determined by HPLC, Chiralcel OJ-H column, C_6H_{14}/Pr^iOH = 95/5, 1.0 mL min^{-1}, 219 nm, t_R 14.01 min, t_S 16.01 min. The absolute configuration of product **18** was determined with account of the optical rotation sign.

use of phosphite **10** containing a 2,5-dimethylpyridinium fragment results in lower enantioselectivity (70% *ee*) and incomplete conversion (see Table 1, run *3*) caused, most likely, by its nonselective coordination.

In summary, we synthesized a novel series of ionic chiral phosphites based on pyridinium and imidazolium ionic liquids. The use of these compounds as ligands in asymmetric Rh-catalyzed hydrogenation results in high enantioselectivity in hydrogenation of both dimethyl itaconate (up to 95% *ee*) and methyl 2-acetamidoacrylate (up to 94% *ee*) with 100% reactant conversion. It is noteworthy that relatively high enantiometric excess in the Rh-catalyzed hydrogenation makes these ligands attractive for testing in other asymmetric processes such as allylic substitution. Moreover, the presence of electrically charged moiety in their molecules makes them suitable for immobilization on solid substrates and in ionic liquids.[7,9]

Experimental

^{31}P, ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 400 instrument (161.98, 400.13 and 100.61 MHz) relative to 85% H_3PO_4 in D_2O and Me_4Si, respectively. The ^{13}C NMR signals were assigned using *J*-modulated spin echo procedure. ESI mass spectra were run on a Finnigan LCQ Advantage instrument. Hydrogenation was carried out on a Parr 4843 reactor equipped with a 25-mL autoclave. The enantiomeric excesses of products **17** and **18** were determined by HPLC on a Varian 5000 chromatograph. Elemental analysis was carried out at the Laboratory of microanalysis of the Institute of Organoelement Compounds. Optical rotation was measured on a Perkin—Elmer-141 polarimeter.

All reactions were carried out under dry argon in anhydrous solvents. The phosphorylating reagent (S_a)-2-chlorodinaphtho-[2,1-*d*:1″,2″-*f*][1,3,2]dioxaphosphepine **8** (see Ref. 10) and the starting complex $[Rh(COD)_2]BF_4$ (see Ref. 11) were prepared by published procedures. Dimethyl itaconate (**15**) and methyl 2-acetamidoacrylate (**16**) were purchased from Aldrich.

Synthesis of ionic substrates 5—7 (general procedure). A mixture of 2-chloroethanol **1** (2.5 g, 31 mmol) and heterocyclic amine (24.8 mmol) was refluxed for 2 h with vigorous stirring at 150 °C under argon. Products **2**—**4** were washed with boiling benzene (4×20 mL), dried *in vacuo* (1 Torr), and used in the next step without further purification. Compounds **2**—**4** (20 mmol) were dissolved in an acetone—ethanol mixture (80 : 20 mL for substrates **2**, **3**) or in acetone (80 mL for substrate **4**), an excess of KBF_4 was added (70 mmol), and the mixture was stirred for 72 h. The solutions thus obtained were filtered through a short column with silica gel, the solvent was evaporated under reduced pressure (40 Torr), and the products were dried for 3 h *in vacuo* (1 Torr).

1-(2-Hydroxyethyl)pyridinium tetrafluoroborate (5). Yield 70%, yellowish oil. Found (%): C, 39.70; H, 4.98; N, 6.44. $C_7H_{10}BF_4NO$. Calculated (%): C, 39.85; H, 4.78; N, 6.64. ^{1}H NMR (DMSO-d_6), δ: 3.85 (t, 2 H, CH_2, J = 4.9 Hz); 4.70 (t, 2 H, CH_2N, J = 4.9 Hz); 5.46 (s, 1 H, OH); 8.17 (t, 2 H, J = 6.8 Hz); 8.62 (t, 1 H, J = 7.8 Hz); 9.07 (d, 2 H, J = 6.2 Hz). ESI MS, m/z (I_{rel} (%)): 124 $[M - BF_4]^+$ (100).

1-(2-Hydroxyethyl)-2,5-dimethylpyridinium tetrafluoroborate (6). Yield 65%, yellowish oil. Found (%): C, 45.45; H, 6.12; N, 5.90. $C_9H_{14}BF_4NO$. Calculated (%): C, 45.23; H, 5.90; N, 5.86. ^{1}H NMR (DMSO-d_6), δ: 2.49 (s, 3 H, CH_3); 2.75 (s, 3 H, CH_3); 3.85 (t, 2 H, CH_2, J = 5.0 Hz); 4.72 (t, 2 H, CH_2N, J = 5.0 Hz); 5.32 (s, 1 H, OH); 7.86 (t, 1 H, J = 6.6 Hz); 8.36 (d, 1 H, J = 7.8 Hz); 8.74 (d, 1 H, J = 5.8 Hz). ESI MS, m/z (I_{rel} (%)): 152 $[M - BF_4]^+$ (100).

1-(2-Hydroxyethyl)-2,3-dimethylimidazolium tetrafluoroborate (7). Yield 72%, yellowish oil. Found (%): C, 37.03; H, 5.93; N, 12.38. $C_7H_{13}BF_4N_2O$. Calculated (%): C, 36.88; H, 5.75; N, 12.29. ^{1}H NMR (DMSO-d_6), δ: 2.58 (s, 3 H, CH_3); 3.70 (t, 2 H, CH_2, J = 4.9 Hz); 3.76 (s, 3 H, CH_3); 4.18 (t, 2 H, CH_2, J = 4.9 Hz); 5.1 (s, 1 H, OH); 7.59 (s, 2 H, 2 CH). ESI MS, m/z (I_{rel} (%)): 141 $[M - BF_4]^+$ (100).

Synthesis of ligands 9—11 (general procedure). Triethylamine (0.2 mL, 1.4 mmol) and the specified ionic synthon (**5**—**7**) (1.4 mmol) were added to a solution of (S_{ax})-2-chlorodinaphtho-[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (**8**) (0.5 g, 1.4 mmol) in CH_2Cl_2 (25 mL), the mixture was stirred for 2 h at 20 °C, and then the reaction solution was washed with water (45 mL). The organic phase was separated, dried over Na_2SO_4, and filtered, and the solvent was evaporated in *vacuo* (40 Torr). The products were purified by flash chromatography on a column with silica gel (CH_2Cl_2, 300 mL).

(R_{ax})-1-[2-(Dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)ethyl]pyridinium tetrafluoroborate (9). Yield 58%, white powder, m.p. 80—83 °C, $[\alpha]_D^{18}$ = −128 (*c* 0.8, CH_2Cl_2). Found (%): C, 61.96; H, 4.29; N, 2.50. $C_{27}H_{21}BF_4NO_3P$. Calculated (%): C, 61.74; H, 4.03; N, 2.67. ^{31}P NMR ($CDCl_3$), δ: 141.25. ^{13}C NMR ($CDCl_3$), δ: 61.7 (s, CH_2); 62.3 (d, CH_2, J = 6.8 Hz); 121.0, 121.1, 122.2, 123.4 (all d, J = 5 Hz); 124.4, 124.4, 125.1 (2 CH, pyridinium); 126.3, 126.4, 126.5, 126.6, 128.2, 128.3, 130.4, 130.5, 130.8, 131.3, 132.0, 132.3, 144.3 (2 CH, pyridinium); 146.3 (CH, pyridinium); 146.4, 147.5 (d, aryl, J = 5 Hz). ESI MS, m/z (I_{rel} (%)): 438 $[M - BF_4]^+$ (100).

(R_{ax})-1-[2-(Dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)ethyl]-2,5-dimethylpyridinium tetrafluoroborate (10). Yield 50%, white powder, m.p. 75—78 °C, $[\alpha]_D^{18}$ = −145 (*c* 1.0, CH_2Cl_2). Found (%): C, 63.12; H, 4.68; N, 2.71. $C_{29}H_{25}BF_4NO_3P$. Calculated (%): C, 62.95; H, 4.55; N, 2.53. ^{31}P NMR ($CDCl_3$), δ: 140.31. ^{13}C NMR, $CDCl_3$: 16.2 (CH_3); 19.4 (CH_3); 58.0 (CH_2); 62.2 (d, CH_2, J = 6.9 Hz); 120.9, 121.0, 122.1, 123.2 (all d, J = 4.7 Hz); 124.2, 124.2, 125.1 (CH, pyridinium); 126.2, 126.3, 126.4, 126.4, 128.2, 128.3, 130.3, 130.5, 130.7, 131.2, 132.0, 132.3, 138,2 (C, pyridinium); 143.2 (CH, pyridinium); 145.4 (CH, pyridinium); 146.3, 147.5 (d, aryl, J = 4.8 Hz); 154.5 (C, pyridinium). ESI MS, m/z (I_{rel} (%)): 466 $[M - BF_4]^+$ (100).

(R_{ax})-1-[2-(Dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)ethyl]-2,3-dimethylimidazolium tetrafluoroborate (11). Yield 65%, white powder, m.p. 70—72 °C, $[\alpha]_D^{19}$ = −132 (*c* 0.9, CH_2Cl_2). Found (%): C, 60.01; H, 4.59; N, 5.31. $C_{27}H_{24}BF_4N_2O_3P$. Calculated (%): C, 59.80; H, 4.46; N, 5.17. ^{31}P NMR ($CDCl_3$), δ: 142.02. 13C NMR ($CDCl_3$), δ: 9.0 (CH_3); 34.6 (CH_3); 48,5 (CH_2); 62.4 (d, CH_2, J = 8.4 Hz); 121.0, 121.2, 122.3, 123.5 (all d, J = 5.5 Hz); 125.1, 125.1, 126.3 (CH, imidazolium); 126.3, 126.3, 126.4, 126.6, 128.3, 128.4, 130.2, 130.6, 130.8, 131.4, 132.1, 132,4, 144.7 (C, imidazolium); 146.6, 147.6 (d, aryl, J = 4.8 Hz). ESI MS, m/z (I_{rel} (%)): 455 $[M - BF_4]^+$ (100).

Synthesis of rhodium complexes 12 and 14 (general procedure). A solution of corresponding ligands **9**—**11** (0.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise over a period of 20 min to a solution of $[Rh(COD)_2]BF_4$ (0.04 g, 0.1 mmol) in CH_2Cl_2 (2 mL), the mixture was stirred for 20 min, the solvent was evaporated *in vacuo* (40 Torr), and the product was washed with ether (2×5 mL) and dried *in vacuo* (1 Torr).

Bis{(R_{ax})-1-[2-(dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)ethyl]pyridinium}(η-(cycloocta-1,5-diene)rhodium(+1) tris(tetrafluoroborate) (12). Yield 94%, orange powder, m.p. 112—121 °C (dec.). Found (%): C, 55.40; H, 4.21; N, 2.02. $C_{62}H_{54}B_3F_{12}N_2O_6P_2Rh$. Calculated (%): C, 55.23; H, 4.04; N, 2.08. ^{31}P NMR ($CDCl_3$), δ: 123.8 (d, J = 260.0 Hz).

Bis{(R_{ax})-1-[2-(dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-yloxy)ethyl]-2,3-dimethylimidazolium}(η-(cycloocta-1,5-diene)rhodium(+1) tris(tetrafluoroborate) (14). Yield 96%, orange powder, m.p. 102—112 °C (dec.). Found (%): C, 54.04; H, 4.51; N, 3.92. $C_{62}H_{60}B_3F_{12}N_4O_6P_2Rh$. Calculated (%): C, 53.87; H, 4.37; N, 4.05. ^{31}P NMR (CH_2Cl_2), δ: 126.7 (d, J = 259.2 Hz).

Asymmetric hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (general procedure). The complex $[Rh(COD)_2]BF_4$ (2.5 mg, 0.006 mmol) and corresponding ligand **9**—**11** (0.012 mmol) or pre-synthesized rhodium complex (**12** or **14**) (0.006 mmol) were dissolved in CH_2Cl_2 (4 mL). Then dimethyl itaconate **15** or 2-acetamidoacrylate **16** (0.6 mmol) was added. The closed autoclave was purged with argon, then purged two times with hydrogen and stirred under a hydrogen pressure of 5 atm. The reaction mixture was diluted with hexane (4 mL) and filtered through a short pad of silica gel. The solvents were evaporated *in vacuo* (40 Torr). The spectroscopic data for asymmetric hydrogenation products **17** and **18** fully correspond to previously published data.[12,13]

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