First chiral phosphite with a quaternary ammonium fragment: synthesis and use in Rh-catalyzed asymmetric hydrogenation

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The first representative of chiral *P*-monodentate phosphite ligands containing quaternary ammonium substituents and its rhodium complex $[Rh(COD)(L)_2]BF_4$ (COD is 1,5-cyclooctadiene) were obtained. The use of this ligand in Rh-catalyzed asymmetric hydrogenation of prochiral methyl esters of unsaturated acids allowed one to achieve optical yields up to 99%.

Key words: phosphites, quaternary ammonium compounds, rhodium complexes, asymmetric hydrogenation, metal complex catalysis, olefins, esters, ligands.

Hydrogenation of prochiral compounds catalyzed by transition metal complexes belongs to the most significant asymmetric transformations because it involves inexpensive molecular hydrogen and produces no side reactions. A further development of this branch necessitates perfection of the ligand pool. First of all, this refers to phosphite-type compounds, which differ from conventional phosphines in synthetic accessibility, oxidation resistance, and high ligating power.[1] It is also important that chiral phosphites are inexpensive. For instance, the price for phosphite derivatives of BINOL (BINOL is 2,2′-dihydroxy-1,1′-binaphthyl) was only 2% of the price of the well-recognized diphosphine ligand BINAP.[2] In recent years, perfect results have been reached by using *P*-monodentate phosphites and phosphoramidites in enantioselective Rh-catalyzed hydrogenation,[1—5] Cu-catalyzed conjugated addition,[6] Ir- and Pd-catalyzed allylation, Pd-catalyzed hydrosilylation—oxidation, and Ru-catalyzed hydrogenation of ketones.[7—10]

The synthesis and catalytic properties of achiral ionic phosphites are well studied (see Ref. 11 and references therein), while data on the use of phosphites as chiral ionic ligands are virtually lacking. The sole example we know is phosphite derivatives of (1*R*,2*R*)-*trans*-diaminocyclohexane containing carbene imidazolium fragments, which have been employed in Pd-catalyzed allylic substitution and Ir-catalyzed hydrogenation.[12] This is an interesting fact since, *e.g.*, optically active cationic phosphinites have been successfully used in asymmetric hydrogenation and allylic substitution.[13,14]

Here we describe the synthesis of chiral *P*-monodentate cationic phosphite from an accessible quaternized amino alcohol and successful use of this ligand in Rh-catalyzed asymmetric hydrogenation.

Results and Discussion

The starting synthon **1** containing an alkylammonium fragment was prepared by quaternization of 2-(dimethylamino)ethanol with heptyl bromide followed by replacement of the counteranion in intermediate product **2** (Scheme 1). Its direct phosphorylation in CH_2Cl_2 gave novel cationic *P*-monodentate chiral phosphite **3**.

Ligand **3** is well soluble in CH_2Cl_2, $CHCl_3$, acetone, and acetonitrile and is fairly resistant to hydrolysis. In particular, it is acceptable to separate compound **3** from its by-product triethylamine hydrochloride by extraction with water from the reaction mixture in CH_2Cl_2.

A reaction of *P*-monodentate phosphite **3** (2 equiv.) with $[Rh(COD)_2]BF_4$ afforded the corresponding cationic rhodium complex **4** (see Scheme 1) identified from ^{31}P NMR, ESI MS, and elemental analysis data (see Experimental).

Phosphite **3** and its complex **4** were tested in Rh-catalyzed asymmetric hydrogenation of esters of prochiral unsaturated acids, namely, methyl itaconate **5** and methyl (*Z*)-2-acetamido-3-phenylacrylate (**6**) (Scheme 2, Table 1). The optical yields of products **7** and **8** were up to 92% and 99%, respectively; the starting reagents were consumed virtually completely. In all the cases, isolated complex **4** provided somewhat higher conversions and optical yields than the catalyst formed *in situ* by a reaction of $[Rh(COD)_2]BF_4$ with ligand **3** in the molar ratio L/Rh = 2. This agrees well with the literature

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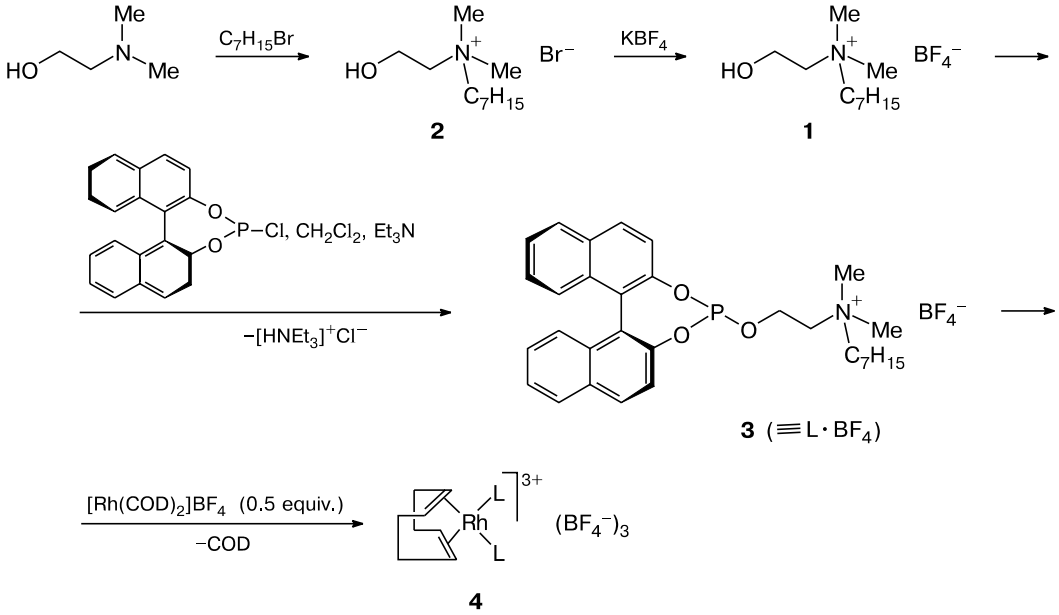
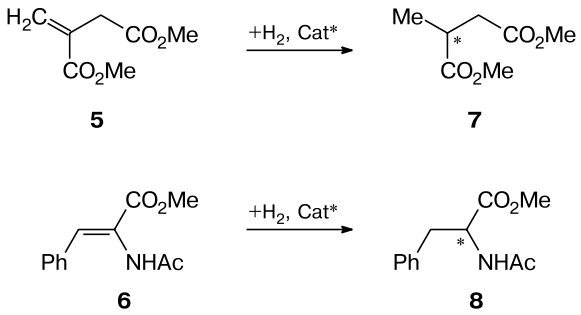
Scheme 1



COD is 1,5-cyclooctadiene

data.[15] Note that the asymmetric induction strongly depends on the solvent nature: in the hydrogenation of compound **5**, *ee* increases by 70% when moving from ethyl acetate to CH_2Cl_2 (see Table 1, entries *2*, *3*).

Scheme 2



Cat is catalyst

Thus, we obtained for the first time a *P*-monodentate chiral phosphite with a quaternary ammonium substituent, which is highly active and enantioselective in the Rh-catalyzed hydrogenation of esters of prochiral unsaturated acids. In addition, the presence of charge on it is attractive for immobilization on solid supports[16] and for use in asymmetric reactions in ionic liquids[17] with possible catalyst recycling.

Experimental

^{31}P, ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker AMX-400 instrument (161.98, 400.13, and 100.61 MHz, respectively) in $CDCl_3$ with reference to 85% H_3PO_4 in D_2O (^{31}P) and Me_4Si (^{1}H, ^{13}C). Signals in the ^{13}C NMR spectra were assigned with the DEPT procedure. ESI mass spectra were recorded on a Finnigan LCQ Advantage instrument. Hydrogenation was carried out on a Parr 4843 setup equipped with a 25-mL autoclave. The optical yields of products **7** and **8** and

Table 1. Rhodium-catalyzed asymmetric hydrogenation of methyl itaconate (**5**) and methyl (*Z*)-2-acetamido-3-phenylacrylate (**6**) (5 atm. H_2, 20 °C, 24 h)

Entry	Substrate	Catalyst	Solvent	Conversion (%)	*ee* (%)
1	**5**	$[Rh(COD)_2]BF_4$/**3**	CH_2Cl_2	80	89 (*S*)
2	**5**	**4**	CH_2Cl_2	98	92 (*S*)
3	**5**	**4**	AcOEt	100	22 (*S*)
4	**6**	$[Rh(COD)_2]BF_4$/**3**	CH_2Cl_2	99	97 (*R*)
5	**6**	**4**	CH_2Cl_2	100	99 (*R*)

their absolute configurations were determined by HPLC on a Varian 5000 chromatograph with a Daicel Chiralcel OD-H chiral column; data[18] were taken into account. Elemental analysis was performed at the organic microanalysis laboratory of the A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

All reactions were carried out under dry argon in anhydrous solvents. The phosphorylating reagent (S_{ax})-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine, the starting complex $[Rh(COD)_2]BF_4$, and methyl (*Z*)-2-acetamido-3-phenylacrylate (**6**) were prepared as described earlier.[19—21] Commercial methyl itaconate (**5**), BINOL, and 2-(dimethylamino)ethanol (Fluka) were used.

***N*-(2-Hydroxyethyl)-*N*,*N*-dimethylheptylammonium tetrafluoroborate (1).** Heptyl bromide (10 g, 56 mmol) was added to a solution of 2-(dimethylamino)ethanol (5 g, 56 mmol) in a mixture of benzene (15 mL) and ethanol (15 mL). The reaction mixture was stirred at 20 °C for 12 h and concentrated *in vacuo* (40 Torr). Bromide **2** was washed with hexane (2×20 mL), dried *in vacuo* (1 Torr), and used in the next step without further characterization. Bromide **2** (10 g, 37 mmol) was dissolved in acetonitrile (30 mL) and refluxed with an excess of KBF_4 (14 g, 111 mmol) while stirring for 48 h. The solution was filtered through a short column with silica gel and concentrated *in vacuo* (40 Torr). The residue was dried *in vacuo* (1 Torr) to give compound **1** (8.652 g, 85%) as white crystals, m.p. 40—43 °C. Found (%): C, 47.86; H, 9.64; N, 5.17. $C_{11}H_{26}BF_4NO$. Calculated (%): C, 48.02; H, 9.52; N, 5.09. ^{1}H NMR, δ: 0.85 (t, 3 H, $^3J_{H,H}$ = 6.8 Hz); 1.24—1.32 (m, 8 H); 1.71 (m, 2 H); 3.23 (s, 6 H); 3.42 (m, 2 H); 3.58 (t, 2 H, $^3J_{H,H}$ = 4.8 Hz); 4.05 (s, 2 H); 4.61 (s, 1 H). ESI MS, *m*/*z* (I_{rel} (%)): 188 $[M - BF_4]^+$ (100), 87 $[BF_4]^-$ (100).

(S_{ax})-*N*-(Dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-2-yloxyethyl)-*N*,*N*-dimethylheptylammonium tetrafluoroborate (3). Triethylamine (0.4 mL, 2.8 mmol) and quaternized amino alcohol **1** (0.784 g, 2.8 mmol) were added to a solution of (S_{ax})-2-chlorodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine (1 g, 2.8 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at 20 °C for 3 h and washed with water (45 mL). The organic phase was separated, dried with Na_2SO_4, filtered, and concentrated *in vacuo* (40 Torr). The product was purified by flash chromatography on silica gel (CH_2Cl_2, 300 mL). The yield of compound **3** was 0.84 g (50%), a white powder, m.p. 80—81 °C. Found (%): C, 63.29; H, 6.16; N, 2.44. $C_{31}H_{37}BF_4NPO_3$. Calculated (%): C, 63.17; H, 6.33; N, 2.38. ^{31}P NMR, δ: 140.1. ^{13}C NMR, δ: 14.0, 22.4, 22.5, 25.8, 28.6, 31.4, 65.6 (C_7H_{15}); 51.5 (s, NMe_2); 58.1 (d, CH_2O, $^2J_{C,P}$ = 8.8 Hz); 63.4 (br.s, CH_2N); 118.2, 121.1, 121.5, 124.6, 125.3, 125.5, 126.6, 126.8, 128.2, 128.6, 129.2, 130.6, 130.8, 131.2, 131.7, 132.4, 132.7, 133.9, 146.8, 147.9 (d, C arom., $^2J_{C,P}$ = 5.1 Hz). ESI MS, *m*/*z* (I_{rel} (%)): 503 $[M - BF_4]^+$ (100), 87 $[BF_4]^-$ (100).

[1,2:5,6-η-(1,5-Cyclooctadiene)],[bis{(S_{ax})-*N*-(dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-2-yloxyethyl)-*N*,*N*-dimethylheptylammonium}]rhodium(1+) tris(tetrafluoroborate) (4). A solution of ligand **3** (0.118 g, 0.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise for 20 min to a solution of $[Rh(COD)_2]BF_4$ (0.04 g, 0.1 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 20 min and concentrated *in vacuo* (40 Torr). The product was washed with ether (2×5 mL) and dried *in vacuo* (1 Torr). The yield of complex **4** was 0.140 g (95%), an orange powder, m.p. 110—121 °C (decomp.). Found (%): C, 57.09; H, 5.67; N, 1.81. $C_{70}H_{86}B_3F_{12}N_2O_6P_2Rh$. Calculated (%): C, 56.93; H, 5.87; N, 1.90. ^{31}P NMR, δ: 124.22 (d, $^1J_{P,Rh}$ = 260.5 Hz). ESI MS, *m*/*z* (I_{rel} (%)): 405 $[M - 3\ BF_4]^{3+}$ (5), 397 $[M - 3\ BF_4 - COD + 2\ MeCN]^{3+}$ (100).

Asymmetric hydrogenation of methyl itaconate (5). Methyl itaconate **5** (0.1 g, 0.6 mmol) was added to a solution of rhodium complex **4** (9.3 mg, 0.006 mmol) in CH_2Cl_2 or ethyl acetate (4 mL). The closed autoclave was purged with argon and then three times with hydrogen. The reaction mixture was stirred under a hydrogen pressure of 5 atm. for 24 h, diluted with hexane (4 mL), and filtered through a short column with silica gel. The solvent was removed *in vacuo* (40 Torr) and the residue was dried *in vacuo* (10 Torr) to give product **7** as a colorless oil. ^{1}H NMR and MS data for compound **7** were in full agreement with the literature data.[22]

Asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-phenylacrylate (6). Compound **6** (0.1 g, 0.46 mmol) was added to a solution of rhodium complex **4** (6.7 mg, 0.0046 mmol) in CH_2Cl_2 (4 mL). The closed autoclave was purged with argon and then three times with hydrogen. The reaction mixture was stirred under a hydrogen pressure of 5 atm. for 24 h, diluted with hexane (4 mL), and filtered through a short column with silica gel. The solvent was removed *in vacuo* (40 Torr) and the residue was dried *in vacuo* (10 Torr) to give product **8** as a white powder. ^{1}H NMR and MS data for compound **8** were in full agreement with the literature data.[22]

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