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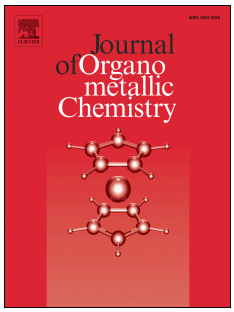

Synthesis of a new bulky phosphite ligand and its application in the enantioselective hydrogenation

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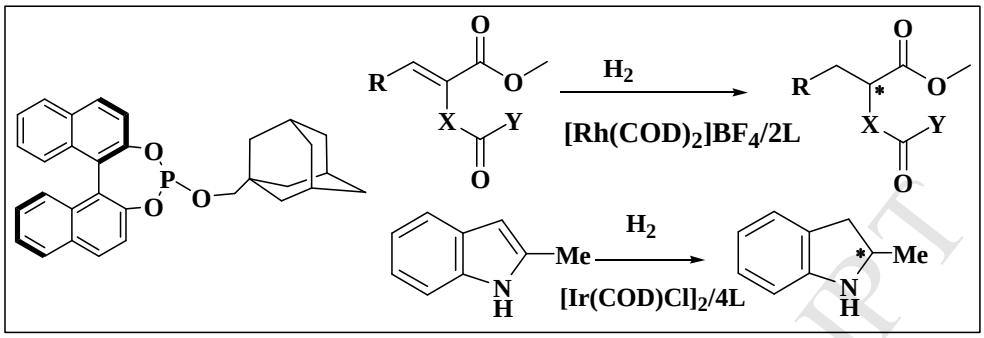
Graphical abstract:



Synopsis.

A new bulky phosphite ligand was synthesized and tested in the asymmetric Rh-catalyzed hydrogenation of a series of substrates, including dimethyl itaconate (up to 95% *ee*), α- and β-dehydroamino acid derivatives (up to 88% and 76% *ee*, respectively).

Synthesis of a new bulky phosphite ligand and its application in the enantioselective hydrogenation.

Marina V. Sokolovskaya[a], Sergey E. Lyubimov[a,*], Igor S. Mikhel[b], Kirill P. Birin[b], Vadim A. Davankov[a]

[a] *A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov Street 28, 119991 Moscow, Russia*

[b] *A.N. Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, Leninskiy prospect 31/4, 119071 Moscow, Russia*

Abstract

A new bulky phosphite ligand was synthesized and tested in the asymmetric Rh-catalyzed hydrogenation of a series of substrates, including dimethyl itaconate (up to 95% *ee*), α- and β-dehydroamino acid derivatives (up to 88% and 76% *ee*, respectively). In the Ir-catalyzed hydrogenation of 2-methylindole, the use of iodine as an additive led to a significant increase in the enantioselectivity and conversion. The best result (64% *ee*) was obtained with $[Ir(COD)Cl]_2$ as precatalyst.

Keywords: asymmetric hydrogenation; amino acids; phosphite ligand; 2-methylindole.

* Corresponding author. Tel.: +7 499 1352548; e-mail: lssp452@mail.ru

1. Introduction.

Enantioselective homogenous hydrogenation catalyzed by chiral transition metal complexes has become one of the most wide-spread methods for obtaining of optically active organic compounds, more commonly utilizing complexes based on Ru, Rh or Ir and including phosphorous-containing chiral ligands.[1] This method is attractive due to low catalyst loadings, high reliability, mild reaction conditions and perfect atom economy. Complexes bearing

phosphine ligands have attracted much attention as a result of their high activity and good enantioselective control.[2] By using ruthenium, rhodium or iridium catalysts with chiral phosphine ligands in the asymmetric hydrogenation of α- and β-dehydroamino acids and heterocyclic compounds, good to excellent enantioselectivities have been obtained.[3,4] However, in the past few years, monodentate phosphites and phosphoramidites were shown to be excellent and sometimes superior alternatives to the phosphine ligands, in terms of enantioselectivity, simplicity of synthesis, stability, ease of structural variation.[5,6] The use of sterically hindered O-alkyl substituents in such ligands is shown to increase stereogenic activity of a metal-complex catalyst in a range of examples.[7-10] Motivated by this observation, we have prepared a novel sterically congested adamantane-containing monodentate phosphite ligand for application in the asymmetric hydrogenation of dimethylitaconate, α- and β-enamides and 2-methylindole.

2. Materials and methods.

2.1. General.

^{31}P, ^{13}C and ^{1}H NMR spectra were recorded with a Bruker Avance 400 (162.0 MHz for ^{31}P, 100.6 MHz for ^{13}C and 400.13 MHz for ^{1}H) and a Bruker Avance III 600 (242.9 MHz for ^{31}P, 150.9 MHz for ^{13}C and 600.13 MHz for ^{1}H) instruments. Complete assignment of all the resonances in ^{1}H and ^{13}C NMR spectra was achieved by the use of DEPT, COSY, ROESY, HSQC, and HMBC techniques. Chemical shifts δ are quoted in parts per million (ppm) downfield of tetramethylsilane. ^{31}P NMR chemical shifts were referenced externally to 85% H_3PO_4 (δ 0.0). Coupling constants J are given in Hz.

NEt_3 was freshly distilled on CaH_2. All other commercially available reagents were used without further purification. Solvents were purified by standard procedures: CH_2Cl_2 and $CDCl_3$ were distilled from CaH_2.

(R_{ax})-2-chlorodinaphtho[2,1-*d*:1',2'-*f*][1,3,2] dioxaphosphepine (**1**)[11], substrates **3b-d**[12-14], **5a**[15] were prepared according to the published procedures. Enamide **5b** was synthesized

analogously to **5a** by refluxing ethyl 3-phenylpropiolate in DMF with catalytic amount of KOH and succinimide.

5b. 52% yield after recrystallization of crude product in Et_2O. White solid, mp 81-82 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): 1.31 (t, *J* = 7.2, 3H, C$\underline{H}_3$), 2.88-3.06 (m, 4H, C$\underline{H}_2$-C$\underline{H}_2$), 4.19 (q, *J* = 7.2, 2H, C$\underline{H}_2$CH$_3$), 6.63 (s, 1H, =CH), 7.36-7.53 (m, 5H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): 14.1 (C$\underline{H}_3$), 29.1 (C$\underline{H}_2$C$\underline{H}_2$), 60.8 (OC$\underline{H}_2$CH$_3$), 117.2 (=C$\underline{H}$), 126.2 (Ph), 129.1 (Ph), 131.1 (Ph), 133.8 (Ph), 144.2 (=C-N), 163.8 (C$\underline{O}$O), 175.9 (C$\underline{(O)}$N). Anal. calcd. for $C_{15}H_{15}NO_4$ C, 65.92; H, 5.53; N, 5.13. Found: C, 66.19; H, 5.76; N, 5.01.

6b. White solid, mp 81-82 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): 1.23 (t, *J* = 7.2 Hz, 3H, C$\underline{H}_3$), 2.67 (br. s, 4H, C$\underline{H}_2$-C$\underline{H}_2$), 3.13 (dd, *J* = 5.6, *J* = 16.4, 1H, CH-C$\underline{H}_2$), 3.76 (dd, *J* = 10.4, *J* = 16.4, 1H, CH-C$\underline{H}_2$), 4.06-4.18 (m, 2H, OC$\underline{H}_2$-CH$_3$), 5.68 (dd, *J* = 5.6 Hz, *J* = 10.4, 1H, C$\underline{H}$N), 7.29-7.39 (m, 3H, Ph), 7.46-7.55 (m, 2H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): 14.1 (C$\underline{H}_3$), 28.0 (C$\underline{H}_2$-C$\underline{H}_2$), 34.8 (NCH-C$\underline{H}_2$), 51.5 (NC$\underline{H}$-CH$_2$), 60.8 (OC$\underline{H}_2$CH$_3$), 128.0 (Ph), 128.3 (Ph), 128.7 (Ph), 138.0 (Ph), 170.6 (C$\underline{O}$O), 177.1 (C$\underline{(O)}$N). Anal. calcd. for $C_{15}H_{17}NO_4$ C, 65.44; H, 6.22; N, 5.09. Found: C, 65.68; H, 6.44; N, 4.91.

Preparation of (R_{ax})-2-(adamantyl-1-ylmethyloxy)-chlorodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine (L).

A solution of 1-adamantylmethanol 174 mg (1.05 mmol) and 0.18 mL (1.3 mmol) NEt_3 in CH_2Cl_2 (5 mL) was added to a vigorously stirred solution of the (R_{ax})-2-chlorodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 368 mg (1.05 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for additional 20 min. The obtained solution was washed with water (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2), the solution was evaporated to give the desired product; yield 413 mg 82%. White solid, mp 113-115 °C. ^{31}P{H} NMR (242.9 MHz, $CDCl_3$): = 143.21. ^{1}H NMR (600.13 MHz, $CDCl_3$): 1.54 (s, 6H, ad), 1.67 (d, *J* = 12.0, 3H, ad), 1.75 (d, *J* = 12.0, 3H, ad), 2.01 (s, 3H, ad),

3.40 (dd, J_{HP} = 7.8 Hz, J_{HH} = 10.2 Hz, 1H, POC<u>H</u>$_2$), 3.60 (dd, J_{HP} = 7.2 Hz, J_{HH} = 10.2 Hz, 1H, POC<u>H</u>$_2$), 7.27-7.31 (m, 2H, ar), 7.39 (d, J = 7.2, 1H, ar), 7.40 (d, J = 7.8, 1H, ar), 7.44-7.48 (m, 1H, ar), 7.45 (t, J = 7.5, 1H, ar), 7.46 (d, J = 9.0, 1H, ar), 7.54 (d, J = 9.0, 1H, ar), 7.95 (d, J = 7.8, 1H, ar), 7.953 (d, J = 7.2, 1H, ar), 7.97 (d, J = 9.0, 1H, ar), 8.00 (d, J =8.4, 1H, ar). ^{13}C NMR (150.9 MHz, $CDCl_3$): 28.10 (C_q, ad), 34.07 (d, J_{CP} = 4.2, OCH$_2$<u>C</u>), 37.03 (CH_2, ad), 39.01 (CH_2, ad), 75.09 (d, J_{CP} = 6.3, O<u>C</u>H$_2$), 121.92 (CH, ar), 121.97 (d, J_{CP} = 1.7, CH, ar), 122.77 (d, J_{CP} = 2.4, C_q, ar), 124.25 (d, J_{CP} = 5.1, C_q, ar), 124.79 (CH, ar), 124.99 (CH, ar), 126.11 (CH, ar), 126.21 (CH, ar), 127.07 (CH, ar), 127.08 (CH, ar), 128.31 (CH, ar), 128.37 (CH, ar), 129.80 (CH, ar), 130.32 (CH, ar), 131.03 (C_q, ar), 131.53 (C_q, ar), 132.69 (d, J_{CP} = 1.2, C_q, ar), 132.90 (d, J_{CP} = 1.5, C_q, ar), 147.70 (d, J_{CP} = 2.1, POC), 148.87 (d, J = 5.1, POC). Anal. calcd. for $C_{31}H_{29}O_3P$ C, 77.48; H, 6.08; P, 6.45. Found: C, 77.75; H, 6.36; P, 6.31.

Synthesis of rhodium complex 2.

A solution of the ligand 0.024 g, (0.050 mmol) in CH_2Cl_2 (0.5 mL) was added to a stirred solution of $[Rh(COD)_2]BF_4$ 0.010 g, (0.025 mmol) in CH_2Cl_2 (0.2 mL). The mixture was stirred for additional 2 min and concentrated at reduced pressure to a volume of ca. 0.15 mL, and hexane (8 mL) was added. The precipitated solid was separated by centrifugation and dried in vacuo. Yellow solid, yield 25.1 mg (92 %). ^{31}P{H} NMR (162.0 MHz, $CDCl_3$): = 120.23 (d, J_{PRh} = 259.0). Anal. calcd. for $C_{70}H_{70}BF_4O_6P_2Rh$ C, 66.78; H, 5.60; P, 4.92. Found: C, 67.02; H, 5.88; P, 4.76.

3. Results and discussion.

A new monodentate phosphite ligand (**L**) was synthesized by a convenient one-step phosphorylation of 1-adamantylmethanol in CH_2Cl_2 (scheme 1).

Scheme 1.

All ^{1}H and ^{13}C NMR signals of **L** were located by a combination of NMR spectroscopic methods (^{1}H, ^{13}C{^{1}H}, ^{13}C{^{1}H} DEPT135, ^{13}C-^{1}H HSQC, ^{13}C-^{1}H HMBC, ^{1}H-^{1}H COSY, and ^{1}H-^{1}H ROESY) (see Figure 1 and Supplementary data for details).

Figure 1.

Reaction of the phosphite ligand with $[Rh(COD)_2]BF_4$ afforded cationic rhodium complex **2** (scheme 2). ^{31}P NMR data for the complex **2** showed chemical shift and coupling constant (see experimental part) similar to those for rhodium complexes with monodentate phosphite ligands.[16,17]

Scheme 2.

The phosphite ligand was firstly used in the Rh-catalyzed hydrogenation of dimethyl itaconate **3a** (Scheme 3).

Scheme 3.

The catalyst was formed *in situ* by mixing $[Rh(COD)_2]BF_4$ with 2 equivalents of the chiral ligand in CH_2Cl_2 under argon. The catalyst exhibited excellent enantioselectivity (95 % *ee*) and complete conversion of **3a** (Table 1, entry 1). The use of isolated complex **2** in the hydrogenation of **3a** showed the same activity and enantioselectivity as the catalyst formed *in situ* (table 1, entry 2). To expand the utility of the ligand, we also examined the Rh-catalyzed enantioselective hydrogenation of α-dehydroamino acids esters: (*Z*)-methyl 2-acetamido-3-phenylacrylate **3b**, (*Z*)-methyl 2-acetamido-3-(4-fluorophenyl)acrylate **3c** and (*Z*)-methyl 2-acetamido-3-(3,4-dimethoxyphenyl)acrylate **3d**. In the hydrogenation of **3b** the ligand showed complete conversion and *ee* up to 82% (Table 1, entry 3). Reduction of the substrate **3c** with electron-withdrawing fluorine-containing substituent on the phenyl ring gave a lower enantioselectivity (76 % *ee*) (Table 1, entry 4). Hydrogenation of a more sterically hindered substrate **3d** with electron-donating methoxy groups gave complete conversion to the *L*-DOPA derivative and 88% *ee* (Table 1, entry 5).

Table 1.

The ligand was also tested in the asymmetric hydrogenation of β-unsaturated amino acid precursors (**5a,b**, scheme 4) containing easy leaving phtalimide and succinimide groups.

Scheme 4.

Firstly we have checked hydrogenation of **5a** in ethanol, 2,2,2-trifluoroethanol and CH_2Cl_2 at 40 °C. A better enantioselectivity was obtained in CH_2Cl_2, the reaction in alcohols showed lower conversion and *ee*`s (table 2, entries 1-3). It should be noted that in the strongly acidic 2,2,2-trifluoroethanol racemic product was obtained. Lowering the temperature from 40 to 25 °C led not only to decrease of reaction rate, but also decrease of enantioselectivity (table 2, entry 4). The hydrogenation of enamide **5b** containing a less bulky succinimide group showed that the process is critically temperature depending. Rising of temperature from 25 to 50 °C led to decrease of selectivity (table 2, entries 5-7).

Table 2.

The ligand was also tested in the iridium catalyzed hydrogenation of 2-methylindole (scheme 5). Using the catalysts prepared *in situ* from $[Ir(COD)Cl]_2$ and the ligand no conversion was obtained (table 3, entry 1). We next examined $[Ir(COD)_2]$BARF as a precatalyst. In this case 31% conversion was obtained, but a low enantioselectivity was observed (table 3, entry 2). Considering remarkable positive impact of addition of iodine in the Ir-catalyzed hydrogenation of heterocyclic compounds[18-21], the hydrogenation of **6** was carried out in presence of iodine (5 mol %). In the case of the catalyst based on $[Ir(COD)_2]$BARF enantiomeric excess was increased up to 16% (table 3, entry 3). The use of $[Ir(COD)Cl]_2$ gave 55 % conversion and 64% *ee* (table 3, entry 4).

Scheme 5.

Table 3.

4. Conclusions.

In conclusion, we have prepared a new bulky phosphite ligand for the use in asymmetric hydrogenation. The ligand proved to be efficient in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate and α- and β-dehydroamino acid derivatives. In the hydrogenation of 2-methylindole the use of iodine as additive led to a significant increase in the enantioselectivity and conversion.

Acknowledgement. This work was supported by RFBR grant № 17-03-00483.

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FIGURES CAPTIONS.

Scheme 1. Ligand synthesis.

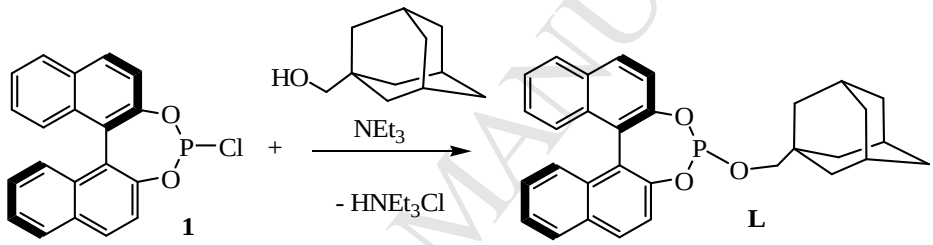
Figure 1. Full assignment of all ^{13}C resonances for ligand **L**.

Scheme 2. Synthesis of rhodium complex**.**

Scheme 3. Rh-catalyzed hydrogenation of **3a-d.**

Scheme 4. Rh-catalyzed hydrogenation of **5a,b**.

Scheme 5. Ir-catalyzed hydrogenation of **7**.



Scheme 1.

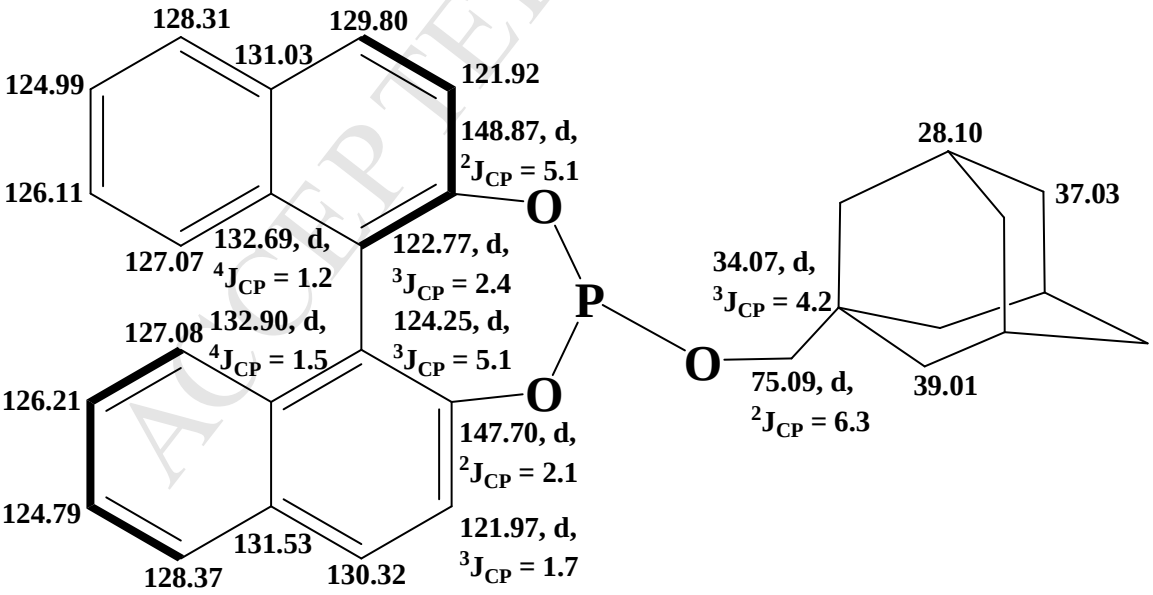
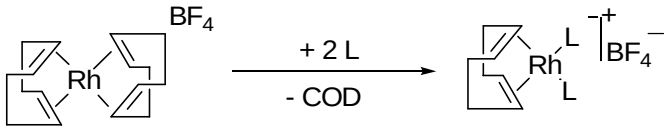


Figure 1.



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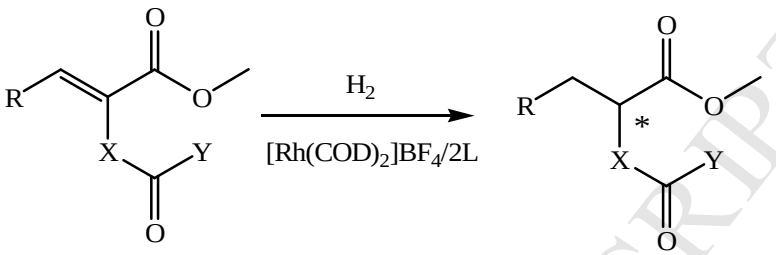
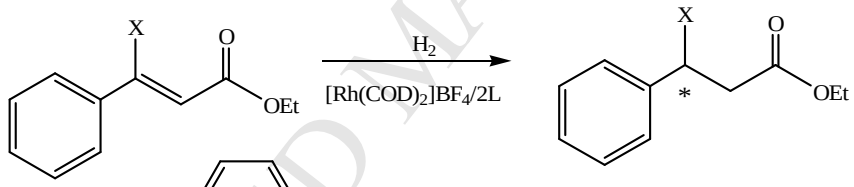
Scheme 2.



3a, R = H, X = CH_2, Y = OMe
3b, R = Ph, X = NH, Y = Me
3c, R = 4-F-Ph, X = NH, Y = Me
3d, R = 3,4-OMe-Ph, X = NH, Y = Me

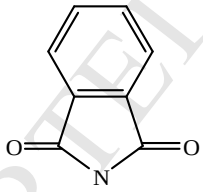
4a-d

Scheme 3.

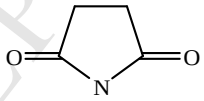


6 a-b

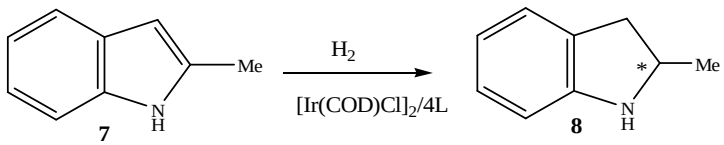
5a X =



5b X =



Scheme 4.



7 **8**

Scheme 5.

Table 1. Asymmetric hydrogenation of **3a-d**.[a]

entry	catalyst	substrate	conversion, %	*ee*, %[b]
1	$[Rh(COD)_2]BF_4$/2**L**	**3a**	100	95 (*R*)
2	**2**	**3a**	100	95 (*R*)
3	$[Rh(COD)_2]BF_4$/2**L**	**3b**	100	82 (*S*)
4	$[Rh(COD)_2]BF_4$/2**L**	**3c**	100	76 (*S*)
5	$[Rh(COD)_2]BF_4$/2**L**	**3d**	100	88 (*S*)

[a] T = 50 °C, P H_2 = 55 atm, t = 2 h, CH_2Cl_2, $[Rh(COD)_2]BF_4$/substrate = 1/100.
[b] determined according to chiral HPLC (see Supplementary data for details).

Table 2. Asymmetric hydrogenation of **5a,b**.[a]

entry	catalyst	substrate	T, °C	t, h	solvent	conversion, %	*ee*, %[b,c]
1	$[Rh(COD)_2]BF_4$/2**L**	**5a**	40	6	EtOH	13	50 (+)
2	$[Rh(COD)_2]BF_4$/2**L**	**5a**	40	6	TFE	16	0
3	$[Rh(COD)_2]BF_4$/2**L**	**5a**	40	6	CH_2Cl_2	100	76(+)
4	$[Rh(COD)_2]BF_4$/2**L**	**5a**	25	24	CH_2Cl_2	44	58 (+)
5	$[Rh(COD)_2]BF_4$/2**L**	**5b**	25	24	CH_2Cl_2	100	34 (+)
6	$[Rh(COD)_2]BF_4$/2**L**	**5b**	40	6	CH_2Cl_2	65	26 (+)
7	$[Rh(COD)_2]BF_4$/2**L**	**5b**	50	6	CH_2Cl_2	75	10 (+)

[a] P H_2 = 55 atm, $[Rh(COD)_2]BF_4$/substrate = 3/100.
[b] Determined according to chiral HPLC (see Supplementary data for details).
[c] The sign of optical rotation given in parenthesis.

Table 3. Asymmetric hydrogenation of **7**.[a]

entry	catalyst	solvent	conversion, %	*ee*, %[b]
1	$[Ir(COD)Cl]_2$/4**L**	CH_2Cl_2	0	-
2	$[Ir(COD)_2]$BARF/2**L**	CH_2Cl_2	31	2 (*S*)
3	$[Ir(COD)_2]$BARF/2**L**/I_2	CH_2Cl_2	7	16 (*S*)
4	$[Ir(COD)Cl]_2$/4**L**/4I_2	CH_2Cl_2	55	64 (*S*)

[a] T = 40 °C, P H_2 = 55 atm, t = 24 h, $[Ir(COD)Cl]_2$/substrate = 1/100.
[b] determined according to chiral HPLC (see Supplementary data for details).

- A new phosphite ligand was tested in the asymmetric Rh- and Ir-catalyzed hydrogenation.
- The ligand showed up to 95% *ee* in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate and α- and β-dehydroamino acid derivatives.
- In the hydrogenation of 2-methylindole the use of iodine as additive led to a significant increase in the enantioselectivity and conversion.