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Synthesis of a chiral pyridylphosphine ligand and a comparison of its rhodium complex with the structurally similar arylphosphine rhodium catalysts in the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid

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Abstract

A chiral pyridylphosphine ligand (2*R*,4*R*)-2,4-bis[di-3′-(2′,6′-dimethoxypyridyl)phosphino]pentane was synthesized. The rhodium catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid was studied by using this ligand in comparison with the structurally similar Skewphos analogs.

1. Introduction

Heterocyclic compounds are an important class of compounds in modern organic chemistry. However, the catalytic property of transition metal complexes containing heterocyclic organophosphines has been relatively unexplored. Rhodium and ruthenium catalysts containing pyridylphosphine ligands have been previously prepared and some of them used in the study of homogeneous catalysis.[1–3] Unfortunately they were found to be inactive in the homogeneous catalytic hydrogenation reactions.[4] The inactivity of the catalysts was thought to be due to the coordination of the pyridyl group which rendered the metal center coordinatively saturated. Recently we have found that by blocking the coordination of the pyridyl group, the resulting rhodium complex Rh-(**1**) was effective for the hydrogenation of olefins, aldehydes and imines.[5] The advantage of pyridylphosphine complexes over regular arylphosphine complexes is that the former can be separated from the organic products via phase separation under acidic conditions. Thus the rhodium complex of **1** has been successfully separated from the hydrogenation products by extracting the catalyst with aqueous hydrochloric acid from a water-immiscible organic solvent.[5] A natural extension

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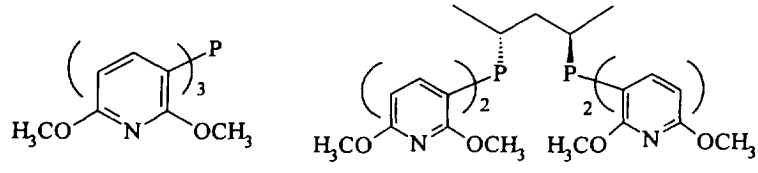
of our success in this study is to incorporate the non-coordinating pyridyl group in chiral skeletons for the development of new chiral pyridylphosphine ligands.

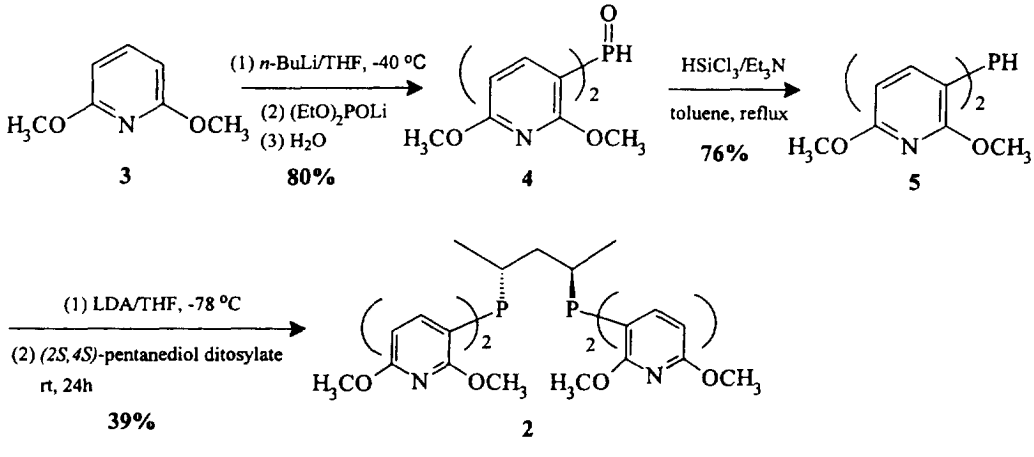


1 2

Herein we report the preparation of a chiral pyridylphosphine (2*R*,4*R*)-2,4-bis[di-3′-(2′,6′-dimethoxypyridyl)phosphino]pentane (**2**) (Py*-Skewphos), in which the PPh_2 moiety of Skewphos is replaced by PPy^*_2 (Py*=2,6-dimethoxypyridine). The asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid catalyzed by rhodium complexes of ligand **2** in comparison with the Skewphos analogs was investigated.

2. Results and discussion

The synthetic route for the preparation of **2** is shown in Scheme 1. The lithiation of the 2,6-dimethoxypyridine (**3**) with *n*-butyllithium at −40°C in THF followed by the addition of lithium diethylphosphide gave bis[3-(2,6-dimethoxypyridyl)]phosphine oxide (**4**) in 80% yield. The reduction of **4** with trichlorosilane in the presence of triethylamine afforded bis[3-(2,6-dimethoxypyridyl)]phosphine (**5**) in good yield. The new, air stable ligand (2*R*,4*R*)-Py*-Skewphos **2** was obtained in 39% yield from the reaction of lithium bis[3-(2,6-dimethoxypyridyl)]phosphide with (2*S*,4*S*)-pentanediol ditosylate.

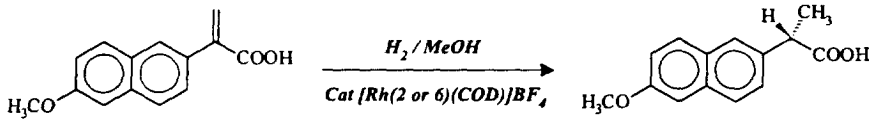


3 4 5 2

Scheme 1.

Naproxen is a nonsteroidal antiinflammatory drug having nonnarcotic analgesic and antipyretic activities.[6] An economically attractive synthetic route for this high-value product was via the catalytic asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid. The use of Ru–(*S*)-BINAP catalysts for this reaction has been demonstrated to be quite successful.[7–9] In our initial study, we tried to prepare the ruthenium complex of **2** via the reaction of **2** with $[Ru(cymene)Cl_2]_2$ in methanol. Unfortunately only one phosphorus in **2** was found to coordinate with the ruthenium metal and the resulting complex was ineffective in the hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid. In this study we focused on the use of the rhodium complex of **2** in the catalytic asymmetric hydrogenation

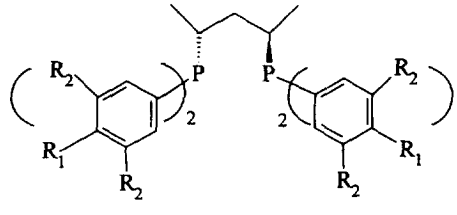
Table 1
Rhodium catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenic acid[a]



Entry	Ligand	P H_2(psi)	Temp.(°C)	H_3PO_4/Cat (M/M)	Time(h)	Conv.(%)	ee(%)[b]	Config.
1	**6a**	200	20	-	12	100	12	*S*
2	**6b**	200	20	-	12	100	13	*S*
3	**6c**	200	20	-	12	18	nd	-
4	**6c**	900	20	-	12	100	<5	*S*
5	**6d**	200	20	-	12	100	26	*S*
6	**6e**	900	20	-	12	100	<5	*S*
7	**2**	200	20	-	12	0	-	-
8	**2**	900	20	-	12	17	nd	-
9	**2**	900	70	-	12	100	28	*S*
10	**2**	900	70	5	16	96	39	*S*
11	**2**	***900***	***70***	***10***	***22***	***100***	***56***	***S***
12	**2**	900	70	20	22	100	33	*S*
13	**6a**	900	20	10	12	50	10	*S*
14	**6a**	900	70	10	12	100	19	*S*
15	**6d**	900	20	10	36	89	5	*S*

[a]The reactions were carried out in methanol with a substrate/rhodium = 100; the catalysts were prepared *in situ* from the ligands **2** or **6** (1.05 equiv) and $[Rh(COD)_2]BF_4$ (1 equiv). [b]The ee values were determined by HPLC using a SUMI CHIRAL OA-2500 column.

of 2-(6′-methoxy-2′-naphthyl)propenic acid. For the purpose of comparison, the Skewphos analogs **6** (all are *R* configurations) were selected and examined in this rhodium catalyzed hydrogenation.



6a : $R_1 = R_2 = H$. **6b** : $R_1 = CH_3$, $R_2 = H$.
6c : $R_1 = CF_3$, $R_2 = H$. **6d** : $R_1 = H$, $R_2 = CH_3$.
6e : $R_1 = H$, $R_2 = CF_3$.

The hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenic acid was carried out in methanol using the catalysts prepared *in situ* from $[Rh(COD)_2]BF_4$ and **2** or **6**. The results of this comparative study clearly showed that the pyridylphosphine **2** was more effective than the corresponding 'Skewphos' type arylphosphine ligands in this Rh-catalyzed asymmetric hydrogenation reaction. The detailed experimental data are summarized in Table 1. The catalytic activity of $[Rh(\mathbf{6})]^+$ was dependent on the electronic effect of the ligand **6**. The electron-withdrawing substituents on the phenyl rings of the phosphine ligands (such as ligands **6c** and **6e**) substantially lowered the catalytic activity of the rhodium

complex, and very low enantioselectivity was obtained in the hydrogenation (Table 1, entries 4 and 6). Ligand **6d** with 3,5-disubstituted methyl groups on the phenyl rings gave somewhat better ee (26%) (Table 1, entry 5).

By using a rhodium catalyst containing ligand Py*-Skewphos **2**, 100% conversion with 28% ee of naproxen product was obtained in the hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid under 900 psi H_2 at 70°C in 12 h (Table 1, entry 9). It is of interest to note that the addition of a certain amount of phosphoric acid to the reaction mixture significantly improved the enantioselectivity of the Rh–(**2**) catalyst system. The addition of 10 equivalents of phosphoric acid [as compared to the Rh(Py*-Skewphos)] gave the best result (100% conversion, 56% ee) (entry 11). In contrast, under otherwise identical conditions, the use of a Rh(Skewphos) type catalyst gave only 19% ee (entry 14). The results of the direct comparison of Py*-Skewphos with Skewphos and its derivatives clearly showed the advantage of the pyridylphosphine in this class of asymmetric catalytic reaction. Obviously a more in-depth study, including the synthesis of (2*R*,4*R*)-2,4-bis[di(2′,4′-dimethoxyphenyl)phosphino]pentane ligand for more accurate comparison, is needed for the elucidation of the key factors of influence and the mechanistic features of the rhodium pyridylphosphine catalyst so that more rational design and improvement of catalyst can be achieved.

In conclusion, we have synthesized a new chiral pyridylphosphine ligand which showed interesting chemistry in the rhodium catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid. The fact that the pyridylphosphine ligand gave substantially better results than the regular aryl analogs was particularly encouraging. It is expected that the exploration of the pyridylphosphine systems will enrich the chemistry of metal–phosphine complexes. The design and synthesis of more effective pyridylphosphine ligands and their application in asymmetric catalytic hydrogenation are in progress.

3. Experimental section

Unless otherwise noted, all reactions were carried out under an inert atmosphere. Melting points were determined using an Electrothermal 9100 apparatus in capillaries sealed under nitrogen and were uncorrected. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter. NMR spectra were recorded on a Bruker DPX-400 spectrometer. Mass analyses were performed by a Finnigan Model Mat 95 ST mass spectrometer. HPLC analyses were performed using a Hewlett–Packard Model HP 1050 LC interfaced to an HP 1050 Series computer workstation.

3.1. Bis[3-(2,6-dimethoxypyridyl)]phosphine oxide (4)

A solution of *n*-butyllithium (62.5 mL of a 1.6M hexane solution, 100 mmol) was added to a solution of 2,6-dimethoxypyridine (13.9 g, 100 mmol) in 200 mL of THF at −40°C under magnetic stirring over a period of 1 h. The resulting mixture was stirred for another 1 h at −40°C and 4 h at ambient temperature. A THF solution (100 mL) of lithium diethylphosphide (50 mmol), which was prepared *in situ* by adding *n*-butyllithium (31.3 mL of a 1.6M hexane solution, 50 mmol) to a THF solution (20 mL) of diethylphosphite (6.7 mL, 50 mmol), was added dropwise to the above solution over a period of 1 h. After stirring for 24 h at room temperature, the reaction was quenched by adding 5 mL of water. The solvent was removed under reduced pressure with a rotary evaporator and the residue was redissolved in 300 mL of ethyl acetate. The ethyl acetate solution was washed with brine (2×50 mL) and dried over anhydrous sodium sulfate. The solution was concentrated to 50 mL and then cooled in a refrigerator overnight. A light yellow solid was collected, which upon recrystallization from ethyl acetate afforded a

white powdery product (12.9 g, 80% theoretical yield). M.p.: 139–140°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.90 (s, 6H), 3.95 (s, 6H), 6.40 (d, J=8.1 Hz, 2H), 7.84 (dd, J_{P-H}=13.5 Hz, J_{H-H}=8.1 Hz, 2H), 8.06 (d, J_{P-H}=515.2 Hz, 1H); ^{31}P-NMR (160 MHz, $CDCl_3$) δ: 4.8 ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 53.5, 53.6, 101.9 (d, J_{P-C}=9.9 Hz), 102.9 (d, J_{P-C}=113.0 Hz), 144.6 (d, J_{P-C}=9.0 Hz), 163.4 (d, J_{P-C}=6.2 Hz), 166.1; IR (KBr): 2997, 2947, 2400, 1593, 1481, 1375, 1333, 1186, 1095, 1010, 933, 807 (cm^{-1}); MS (30 eV): *m/z* 325 (M^++1), 294, 152.

3.2. *Bis[3-(2,6-dimethoxypyridyl)]phosphine (5)*

A toluene solution (100 mL) of **4** (5.0 g, 15.4 mmol), triethylamine (10 mL, 72 mmol) and trichlorosilane (7.2 mL, 72 mmol) was stirred at reflux temperature for 12 h. The reaction mixture was allowed to cool to room temperature. A 15% NaOH solution (20 mL) was added and the mixture was stirred at reflux temperature for 4 h. The aqueous layer was separated from the organic phase and was extracted with toluene (2×20 mL). The combined organic solution was dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give a white solid which was washed with methanol to afford **5** (3.6 g, 76% theoretical yield). M.p.: 113–114°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 6H), 3.95 (s, 6H), 5.05 (d, J_{P-H}=229.5 Hz, 1H), 6.26 (d, J=7.9 Hz, 2H), 7.48 (dd, J_{P-H}=6.4 Hz, J_{H-H}=7.9 Hz, 2H); ^{31}P-NMR (160 MHz, $CDCl_3$) δ: −78.8 ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 54.2, 54.3, 102.0, 105.5 (d, J_{P-C}=112.4 Hz), 147.5 (d, J_{P-C}=12.5 Hz), 164.3 (d, J_{P-C}=10.0 Hz), 164.8; IR (KBr): 3006, 2960, 2914, 2315, 2256, 1578, 1485, 1460, 1420, 1380, 1275, 1249, 1189, 1104, 887, 814 (cm^{-1}); MS (30 eV): *m/z* 309 (M^++1).

3.3. *(2R,4R)-2,4-Bis[di-3′-(2′,6′-dimethoxypyridyl)phosphino]pentane (2)*

LDA (1.8 mL of a 2.0M THF solution, 3.6 mmol) was slowly added to a 15 mL of a THF solution of **5** (0.86 g, 2.80 mmol) at 0°C with magnetic stirring over a period of 0.5 h. After stirring for another 2 h, 10 mL of a THF solution of (2*S*,4*S*)-pentanediol ditosylate (0.58 g, 1.4 mmol) was added dropwise at that temperature. The reaction mixture was allowed to warm to room temperature and stirred for another 20 h. The reaction was quenched by adding 0.5 mL of 1N HCl. The solvent was removed under reduced pressure with a rotary evaporator and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (15 mL), brine (15 mL), and then dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave a crude material which was purified through a silica gel column (hexane:ethyl acetate=4:1) to afford white solid **2** (0.45 g, 39% theoretical yield). M.p.: 85–87°C; $[\alpha]_D^{20}$=+44.3 (c=1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.98 (dd, J_{P-H}=16.8 Hz, J_{H-H}=6.8 Hz, 6H), 1.25 (m, 2H), 2.83 (m, 2H), 3.80 (s, 6H), 3.85 (s, 6H), 3.89 (s, 6H), 3.90 (s, 6H), 6.23 (d, J=7.9 Hz, 2H), 6.27 (d, J=8.0 Hz, 2H), 7.57 (m, 4H). ^{1}H-NMR {^{31}P} ($CDCl_3$) δ: 0.98 (d, J=6.8 Hz, 6H), 1.25 (m, 2H), 2.83 (m, 2H), 3.80 (s, 6H), 3.85 (s, 6H), 3.89 (s, 6H), 3.90 (s, 6H), 6.23 (d, J=7.9 Hz, 2H), 6.27 (d, J=8.0 Hz, 2H), 7.55 (d, J=8.0 Hz, 2H), 7.58 (d, J=7.9 Hz, 2H); ^{31}P-NMR (160 MHz, $CDCl_3$) δ: −26.5ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 1.7, 16.1, 25.2 (d, J_{P-C}=21.7 Hz), 54.1, 54.3, 102.2, 145.3, 147.5, 165.1, 165.2, 165.3; IR (KBr): 2954, 2863, 1586, 1487, 1452, 1375, 1312, 1087, 1010 (cm^{-1}); MS (30 eV): 685 (100%, M^++1); HRMS (ESI) *m/z* 685.2520 (MH^+, exact mass calcd for $C_{33}H_{43}P_2N_4O_8$ 685.2556).

3.4. *General procedure for the hydrogenation reaction*

In an inert atmosphere glovebox, a stainless steel reactor was charged with 2-(6′-methoxy-2′-naphthyl)propenoic acid (5 mg, 0.0219 mmol), catalyst (21.9 μL of a 0.01M methanol solution) generated *in situ* by adding the diphosphine ligand (0.0105 mmol) to $[Rh(COD)_2]BF_4$ (4.1 mg, 0.01 mmol) in 1

mL of methanol. The mixture was diluted to 2.5 mL by further addition of methanol. The reactor was closed and was pressurized to the pre-determined pressure of H_2 and stirred at a pre-set temperature. The conversion and enantiomeric excess of naproxen was determined by HPLC.

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