Highly Effective Chiral Dipyridylphosphine Ligands: Synthesis, Structural Determination, and Applications in the Ru-Catalyzed Asymmetric Hydrogenation Reactions

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Heteroaromatic compounds constitute an important class of synthetic and natural products. The chemistry involving this class of compounds is so rich that the subject has become a major branch in organic chemistry. However, the catalytic property of transition-metal complexes containing heteroaromatic organophosphines has been relatively unexplored. Recently Benincori et al.[1,2] and Tietz et al.[3] developed a series of substituted bithiophene- and bibenzo[*b*]thiophene-containing chiral phosphines and found them to be effective in asymmetric hydrogenation and Heck reactions. Rhodium and ruthenium catalysts containing pyridylphosphine ligands have been previously prepared, and some of them have been tested in homogeneous catalysis.[4] Unfortunately, the tested complexes were found to be inactive in the homogeneous hydrogenations.[5] The inactivity of the catalysts was attributed to the pyridyl group which coordinated to the metal center and rendered the complex coordinately saturated. Recently, we have observed that by intentionally blocking the coordination of the pyridyl groups via the use of bulky substituents, the resulting rhodium(I) complex was effective for the hydrogenation of olefins, aldehydes, and imines.[6] Furthermore, the solubility of the new ligands, either in aqueous or in organic solvents, can be easily controlled simply by adjusting the acidity of the solution. Separation of the catalyst from the reaction product in a water-immiscible organic solvent was achieved by extracting the catalyst with aqueous hydrochloric acid; the complex remained intact during the extraction process.[6a]

Building on the success of the modified pyridylphosphine and expanding the scope of study to the area of asymmetric catalysis, we have developed a class of highly effective chiral heteroaromatic ligands. Herein, we report the synthesis, characterization, and application of a new class of chiral pyridylphosphine ligand, 2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine (**P**-phos).

The synthetic route for **P**-phos ligand is outlined in Scheme 1. The slow addition of bromine to commercially available 2,6-dimethoxypyridine (**1**) in carbon tetrachloride at a temperature between −30 and −40 °C provided 3-bromo-2,6-dimethoxypyridine (**2**) in 76% yield.[7] The regioselective lithiation[8] of **2** with lithium diisopropylamide (LDA) in THF at −78 °C, followed by the addition of chlorodiphenylphosphine produced 3-bromo-2,6-dimethoxy-4-diphenylphosphino-pyridine (**3**, 95% yield). The phosphine was converted to 3-bromo-2,6-dimethoxy-4-diphenylphosphinylpyridine (**4**) by mixing with hydrogen peroxide in acetone at 0 °C (96% yield). The racemic dipyridylphosphine oxide **5** was obtained via Ullmann coupling[9] of **4**. The enantiomers of **5** were obtained via resolution with a preparative chiral column.[10] The structure of (*S*)-dipyridylphosphine oxide was determined by single crystal X-ray diffraction. Subsequent reduction of enantiomerically pure **5** with trichlorosilane in the presence of triethylamine led to the targeted enantiomers of atropisomeric ligands **7** which was characterized by ^{1}H, ^{31}P NMR, elemental analysis, high-resolution mass spectrometry, and an X-ray diffraction study of its Ru complex. The enantiomeric purity of the ligand was verified via its oxidation to the known phosphine oxide form (**5**) followed by HPLC analysis. Although an attempt to resolve racemic **5** by (−)-dibenzoyl-L-tartaric acid ((−)-DBT) or (1*S*)−(+)-camphorsulfonic acid was unsuccessful, we found that the production of optically pure ligand **7** can be achieved via the conversion of racemic **5** to the dibromo-derivative **6**,[11] which can be resolved by (−)-DBT or (+)-DBT,[12] followed by reduction with trichlorosilane. All of the synthetic intermediates are air-stable, and the overall synthesis steps are easy to handle. Unlike many bipyridines which racemize easily,[13] these new ligands are optically stable even at elevated temperature. (No racemization was observed at 120 °C).

The new ligand can be used to make discrete transition-metal complexes without the complication of the coordination of the pyridyl rings. For example, Ru(*R*-**P**-phos)(acac)$_2$ was prepared by mixing *R*-**P**-phos with Ru(acac)$_3$ (acac = acetylacetonate) in the presence of a reducing agent, and the complex was characterized by ^{1}H, ^{31}P NMR, elemental analysis, and X-ray crystallography.

$$\mathrm{Ru(acac)_3} \xrightarrow[\text{EtOH, reflux}]{\textit{R}\text{-P-phos, Zn powder,}} \mathrm{Ru}(\textit{R}\text{-P-phos})(\mathrm{acac})_2 \quad 97\%\ \text{yield}$$

Ru(*R*-**P**-phos)(acac)$_2$ was tested in the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid as an economically attractive reaction for the preparation of the nonsteroidal antiinflammatory drug naproxen.[14] It is worth noting that while there are many good catalysts for the asymmetric hydrogenation of α-amidoacrylic acids leading to amino acids in high ee, very few catalysts are effective in the asymmetric hydrogenation of 2-arylacrylic acids.[1,2,15] Since naproxen is a large-volume, high-value product, a good catalyst for this reaction is of substantial interest. The experimental results are summarized in Table 1. The addition of a small amount of phosphoric acid to the reaction mixture improved the ee by one to two percent (entry 4 vs 5, 6 vs 7). In the presence of 0.6 equiv of phosphoric acid at 0 °C

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(10) The enantiomers of **5** were separated by HPLC with a preparative Daicel AD column (25 m × 1.2 m). Eluent = 2-propanol:hexane (20:80); flow rate = 3.0 mL/minute; t_R = 12.24 min; t_S = 25.06 min.
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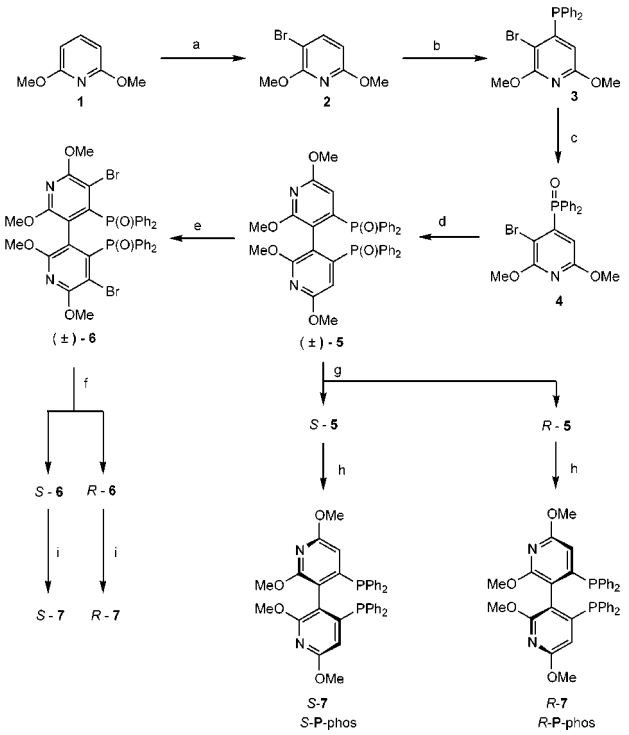
Scheme 1[a]



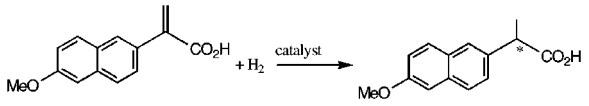
[a] (a) Br_2, CCl_4, −30 ∼−40 °C, 75.6%; (b) LDA, THF, −78 °C, then $ClPPh_2$, −78 °C, 95%; (c) H_2O_2, acetone, 0 °C, 96%; (d) Cu, DMF, 140 °C, 80%; (e) Br_2, NaOAc, HOAc, 0−60 °C, 97%; (f) resolved by (+)- or (−)-DBT, EA/$CHCl_3$ = 1/1; (g) resolved by a preparative Daicel AD column; (h) Cl_3SiH, NEt_3, toluene, 140 °C, 99%; (i) Cl_3SiH, NEt_3, toluene, RT to 140 °C, 91%.

and under 1000 psi H_2, the desired naproxen product was obtained in 96.2% ee This compared favorably with the Ru(BINAP) catalyst system which gave 94.8% ee in a side-by-side comparison study (entry 2 vs 7). The addition of phosphoric acid has very little effect on the Ru(BINAP) catalyst system (entry 1 vs 2).

When Ru[(*S*-**P**-phos)$Cl_2(DMF)_n$] catalyst was applied to the asymmetric hydrogenation of β-ketoesters, the enantioselectivities of the products were also found to be very high (Table 2) and compared favorably with the Ru(BINAP) system.[16]

In conclusion, we have designed and prepared a new class of chiral atropisomeric dipyridylphosphine ligand (**P**-phos) via an easily handled synthetic route. This ligand forms well-defined ruthenium complexes that offer high enantioselectivities in the catalytic hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid and β-ketoesters. Further exploration of the general application of this class of ligands in asymmetric catalytic reactions is in progress.

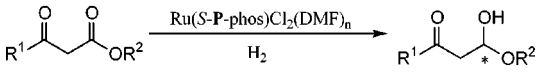
Table 1. Ru(*R*-**P**-phos)-catalyzed Asymmetric Hydrogenation[17] of 2-(6′-Methoxy-2′-naphthyl)propenoic Acid[a]



entry	catalyst	additive	*P* (psi)	*T* (°C)	ee (%)[b]	config.
1	Ru(*S*-BINAP)(acac)$_2$	−	1000	0	94.6	*S*
2	Ru(*S*-BINAP)(acac)$_2$	H_3PO_4[c]	1000	0	94.8	*S*
3	Ru(*R*-**P**-phos)(acac)$_2$	−	500	RT	86.8	*R*
4	Ru(*R*-**P**-phos)(acac)$_2$	−	1000	RT	91.5	*R*
5	Ru(*R*-**P**-phos)(acac)$_2$	H_3PO_4[c]	1000	RT	93.6	*R*
6	Ru(*R*-**P**-phos)(acac)$_2$	−	1000	0	95.3	*R*
7	Ru(*R*-**P**-phos)(acac)$_2$	H_3PO_4[c]	1000	0	96.2	*R*

[a] Reaction conditions: substrate/catalyst = 200−800 (M/M); substrate concentration = 2.0 (mg/mL); reaction time = 13−18 h; solvent = MeOH (2.5 mL); complete conversion was observed in all cases. [b] The ee values were determined by chiral HPLC with a Sumi-chiral OA-2500 column. [c] H_3PO_4/substrate = 0.6 (M/M).

Table 2. Asymmetric Hydrogenation[a] of β-ketoesters Catalyzed by Ru[(*S*-**P**-phos)$Cl_2(DMF)_n$][18]



entry	R^1	R^2	*T* (°C)	*S*/*C* (M/M)	ee (%)
1[b]	Me	Me	70	400	98.5
2[b]	Me	Et	70	400	98.6
3[c]	Me	CH_2Ph	80	2800	96.6
4[c]	Et	Me	80	2800	98.0
5[b]	CH_2Cl	Et	80	2800	98.0
6[d]	Ph	Et	90	2400	95.2 (85)[e]

[a] Reaction conditions: 50 psi H_2; 100 mg substrate; substrate concentration = 0.1−0.17 M in MeOH/CH_2Cl_2 or EtOH/CH_2Cl_2; 12−36 h reaction time; complete conversion was obtained in all cases.[b] The ee values were determined by chiral GC with a Chrompack WCOT fused silica 25 m × 0.25 mm coating CP Chirasil-DEX CB column after converting the products to the corresponding acetyl derivatives. [c] The ee's were determined by chiral GC with a Chiraldex G-PN column after converting the products to the corresponding acetyl derivatives. [d] 17.6 g of substrate was used; solvent = EtOH (10 mL) + CH_2Cl_2 (10 mL). [e] The number in bracket (85% ee) was from the $RuBr_2$(BINAP)-catalyzed reaction.[16]

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Supporting Information Available: Crystallographic data for the compounds S-**5** and Ru(R-**P**-phos)(acac)$_2$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The general procedure for the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid: A glass-lined stainless steel autoclave was charged with 5.00 mg 2-(6′-methoxy-2′-naphthyl)propenoic acid, 0.10 mg Ru(*R*-**P**-phos)(acac)$_2$ and 2.50 mL methanol under nitrogen atmosphere. The mixture was stirred well with a magnetic stirrer under different conditions. The conversion and the enantiomeric excess of naproxen were determined by chiral HPLC with a Sumichiral OA-2500 column.

(18) The general procedure for the asymmetric hydrogenation of β-ketoesters: A glass-lined stainless steel autoclave was charged with 100 mg β-ketoesters, 0.50 mg Ru[(*S*-**P**-phos)$Cl_2(DMF)_n$] (in 0.5 mL MeOH/CH_2Cl_2-(10:1)), and 4.5 mL methanol under nitrogen atmosphere. The mixture was stirred well with a magnetic stirrer at the set temperature (e.g., 70 or 80 °C). The conversion and the enantiomeric excess were determined by chiral GC after converting the products to the corresponding acetyl derivatives.